BENZOIC AND PHENYL ACETIC ACID DERIVATIVES AS HNF-4α MODULATORS

RELATED APPLICATIONS

[001] This application claims the benefit of priority of U.S. Provisional Application Ser. No. 60/487,915 filed July 16, 2003, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

[002] This invention relates to compounds that bind to and/or modulate hepatocyte nuclear factor 4α receptors and to methods for making and using such compounds.

BACKGROUND

[003] Hepatocyte nuclear factor 4α (HNF-4α) has been described as a member of the steroid/thyroid superfamily of transcription factors that is expressed in liver, kidney, intestine and pancreas. Sladek, *et al.* (1990) *Genes Dev.* 4:, 2353-2365; Miquerol, *et al.* (1994) *J. Biol. Chem.* 269: 8944-8951. No ligand has been identified at present and therefore HNF-4α is referred to as an orphan member of the intracellular receptor family (3-5). Tsai, O'Malley, (1994) *Annu. Rev. Biochem.* 63: 451-486; Mangelsdorf, Evans, . (1995) *Cell* 83, 841-850; Kastner, *et al.* (1995) *Cell* 83: 859-869.

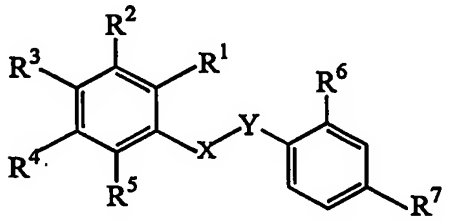
[004] HNF-4α has been described as being capable of activating transcription in tissue culture cells under certain conditions. Kou *et al*, (1992) *Nature* 355:457-461; Ladias *et al*, (1992) *J. Biol. Chem.* 267:15849-15860; Mietus-Snyder *et al*, (1992) *Mol. Cell. Biol.* 12:1708-1718; Metzger *et al*, (1993) *J. Biol. Chem.* 268:16831-16838. It has

been suggested that HNF-4α plays a role in one or more metabolic pathways, including glucose and lipid homeostasis. Ladias, *et al*, (1992) *J. Biol. Chem.* **267**:15849-15860; Mietus-Snyder *et al*, (1992) *Mol. Cell. Biol.* **12**:1708-1718; Metzger *et al*, (1993) *J. Biol. Chem.* **268**:16831-16838; Yamagata *et al*, (1996) *Nature* **384**: 458-460; Stoffel & Duncan (1997) *Proc. Natl. Acad. Sci. U.S.A.* **94**:13209-13214.

[005] Certain mutations of HNF-4α result in defective function of the endocrine pancreas and maturity-onset diabetes of the young (MODY1), suggesting that HNF-4 α plays a role in metabolic gene regulation. Yamagata *et al*, K (1996) *Nature* **384**:458-460. Liver-specific knockouts demonstrate that HNF-4α plays a role in liver development and function. Li *et al*, (2000) *Genes & Dev.* **14**:464-474; Hayhurst *et al*, (2001) *Mol. Cell. Biol.* **21**:1393-1403; Fraser *et al*, (1998) *Nuc. Acids Res.* **26**:2702-2707.

SUMMARY OF THE INVENTION

[006] In certain embodiments, the present invention provides a compound of formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein:

R^1 is selected from H, a halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, and C_2-C_4 alkynyl optionally substituted with one or more halogens;

R^2 and R^4 are each independently selected from H, a halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_3 alkoxy optionally substituted with one or more halogens, a carbocyclic or heterocyclic ring optionally substituted with one or more halogens, a nitro, and a $NR^{13}R^{14}$; or

R^1 and R^2 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15};

R^3 is selected from H, a halogen, an acyl, a methyl optionally substituted with one or more halogens, and a methoxy optionally substituted with one or more halogens; or

R^2 and R^3 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}; or

R^3 and R^4 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15};

R^5 is selected from H, a halogen, a C_1-C_6 optionally substituted with one or more halogens, a C_2-C_6 alkenyl optionally substituted with one or more halogens, a C_2-C_6 alkynyl optionally substituted with one or more halogens, C_1-C_5 alkoxy optionally

substituted with one or more halogens, C_1-C_5 thioalkyl optionally substituted with one or more halogens, a C_2-C_5 alkenyl optionally substituted with one or more halogens, C_2-C_5 alkynyl optionally substituted with one or more halogens a carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}, an acyl, a nitro, and a $NR^{16}R^{17}$; or

R^4 and R^5 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15};

R^6 is selected from H, a halogen, a methyl optionally substituted with one or more fluorines and a methoxy;

R^7 is selected from a CH_2OH, CHO, a carboxylic acid or a $(C(R^9)(R^{10}))_nCO_2H$ or a $(C(R^9)(R^{10}))_nCO_2(CH_2)_mCH_3$, wherein n is 0, 1, or 2; and m is 0, 1, or 2;

R^9 and R^{10} are each independently selected from H, F, and OH; or R^9 and R^{10} taken together form an oxygen;

R^{13} and R^{14} are each independently selected from H, a C_1-C_5 alkyl optionally substituted with one or more halogens, a C_2-C_5 alkenyl optionally substituted with one or more halogens, a C_2-C_5 alkynyl optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more halogens; or R^{13} and R^{14} taken together with the nitrogen to which they are each bound to form a five to eight-membered heterocyclic ring;

R^{15} is selected from H, a halogen, NO_2, a cyano, an acyl, a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, a C_2-C_3 alkynyl optionally substituted with one or more halogens a C_1-C_2

alkoxy optionally substituted with one or more halogens, C_1-C_2 thioalkyl optionally substituted with one or more halogens, a C_2 thioalkenyl optionally substituted with one or more halogens, and a C_2 thioalkynyl optionally substituted with one or more halogens;

R^{16} and R^{17} are each independently selected from H, a C_1-C_5 alkyl optionally substituted with one or more halogens, a C_2-C_5 alkenyl optionally substituted with one or more halogens, a C_2-C_5 alkynyl optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more R^{15}; and

X and Y are each independently selected from a methylene optionally substituted with one or more halogens, a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, C_2 alkynyl optionally substituted with one or more halogens, O, S, a NR^{18}, and benzyl optionally substituted with one or more fluorines, wherein

if X is methylene, then Y is selected from NR^{18}, O and S;

if Y is methylene, then X is selected from NR^{18}, O and S; and

R^{18} is selected from H a C_1-C_5 alkyl, a C_2-C_6 alkenyl, and aC_2-C_6 alkynyl.

[007] In certain embodiments, the invention provides a pharmaceutical agent comprising a pharmaceutically acceptable carrier and a compound of Formula I.

[008] In certain embodiments, the invention provides a method of treating a patient comprising administering to said patient a pharmaceutical agent comprising a

pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of Formula I.

[009] In certain embodiments, the invention provides a selective HNF-4α modulator of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

[010] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting.

[011] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

Definitions

[012] Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, medicinal chemistry and pharmaceutical chemistry described herein are those known in the art. Standard chemical symbols are used interchangeably with the full names represented by such symbols. Thus, for example,

the terms "hydrogen" and "H" are understood to have identical meaning. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques may be used for recombinant DNA methodology, oligonucleotide synthesis, tissue culture and transformation (*e.g.*, electroporation, lipofection). Reactions and purification techniques may be performed *e.g.*, using kits according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general or more specific references that are cited and discussed throughout the present specification. *See e.g.*, Sambrook *et al. Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

[013] As used herein, the following terms are defined with the following meanings:

[014] The term "selective binding compound" refers to a compound that selectively binds to any portion of one or more target receptors.

[015] The term "selective HNF-4α receptor binding compound" refers to a compound that selectively binds to any portion of an HNF-4α receptor.

[016] The term "selectively binds" refers to the ability of a selective binding compound to bind to a target receptor with greater affinity than it binds to a non-target receptor. In certain embodiments, selective binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity for a non-target.

[017] The term "target receptor" refers to a receptor or a portion of a receptor capable of being bound by a selective binding compound. In certain embodiments, a target receptor is an HNF-4α receptor.

[018] The term "modulator" refers to a compound that alters or elicits an activity of a molecule. For example, a modulator may cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[019] The term "selective modulator" refers to a compound that selectively modulates a target activity.

[020] The term "selective HNF-4 α receptor modulator" refers to a compound that selectively modulates at least one activity associated with an HNF-4a receptor.

[021] The term "selectively modulates" refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity.

[022] The term "target activity" refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, changes in binding affinity, signal transduction, enzymatic activity, transcription of one or more genes, tumor growth, changes in blood glucose concentration, and inflammation or inflammation-related processes.

[023] The term "receptor-mediated activity" refers to any biological activity that results, either directly or indirectly, from binding of a ligand to a receptor.

[024] The term "agonist" refers to a compound, the presence of which results in a biological activity of a receptor that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the receptor.

[025] The term "partial agonist" refers to a compound the presence of which results in a biological activity of a receptor that is of the same type as that resulting from the presence of a naturally occurring ligand for the receptor, but of a lower magnitude.

[026] The term "antagonist" refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a receptor. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a receptor. The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

[027] The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl and the like.

[028] The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon tyriple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.In certain embodiments, an alkyl comprises 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that an alkyl group may comprise only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms, although the term "alkyl" also includes instances where no numerical range of carbon atoms is designated).

[029] The term "lower alkyl" refers to an alkyl comprising 1 to 6 carbon atoms. The term "medium alkyl" refers to an alkyl comprising 7 to 12 carbon atoms. An alkyl may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl", "C_1-C_4 alkenyl" and"C_1-C_4 alkynyl" indicate a radical having one, two, three, or four carbon atoms (*e.g.*, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl).

[030]

[031] The term "haloalkyl" refers to an alkyl in which at least one hydrogen atom is replaced with a halogen atom. In certain of the embodiments in which two or more hydrogen atom are replaced with halogen atoms, the halogen atoms are all the same as each other. In certain of such embodiments, the halogen atoms are not all the same as each other.

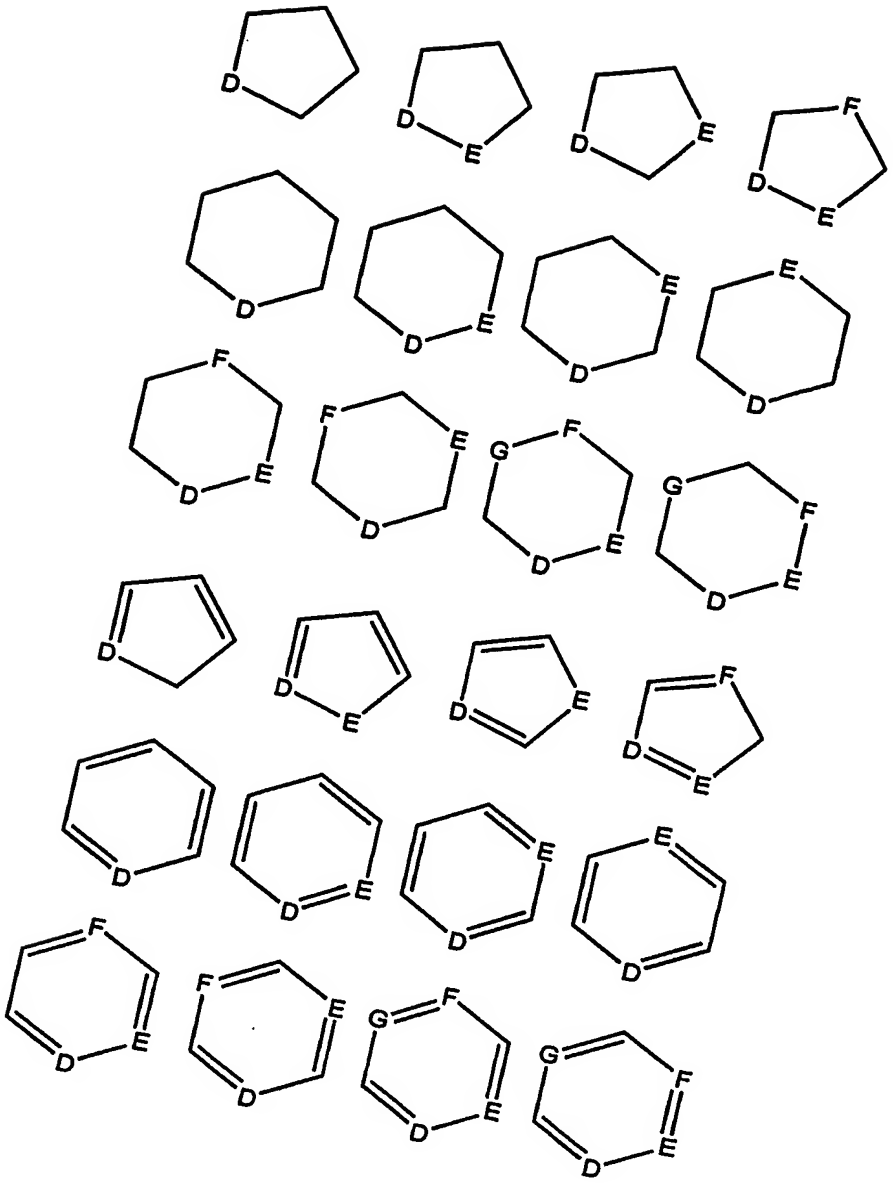
[032] The term "heteroalkyl" refers to a group comprising an alkyl and one or more heteroatoms. Certain heteroalkyls are acylalkyls, in which the one or more heteroatoms are outside an alkyl chain. Examples of heteroalkyls, heteroalkenyl, and heteroalkynyls include, but are not limited to, $CH_3C(=O)CH_2$-, $CH_3C(=O)CH_2CH_2$-, $CH_3CH_2C(=O)CH_2CH_2$-, $CH_3C(=O)CH_2CH_2CH_2$-, $CH_3OCH_2CH_2$-, CH_3NHCH_2-, and the like.

[033] The term "thioalkyl" refers to a heteroalkyl comprising at least one sulfur atom.

[034] The term "heterohaloalkyl" refers to a heteroalkyl in which at least one hydrogen atom is replaced with a halogen atom.

[035] The term "carbocycle" refers to a group comprising a covalently closed ring, wherein each of the atoms forming the ring is a carbon atom. Carbocylic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles may be optionally substituted.

[036] The term "heterocycle" refers to a group comprising a covalently closed ring wherein at least one atom forming the ring is a heteroatom. Heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Any number of those atoms may be heteroatoms (i.e., a heterocyclic ring may comprise one, two, three, four, five, six, seven, eight, nine, or more than nine heteroatoms). In heterocyclic rings comprising two or more heteroatoms, those two or more heteroatoms may be the same as or different from each other. Heterocycles may be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. For example, binding for benzo-fused derivatives, may be via a carbon of the benzenoid ring. Examples of heterocycles include, but are not limited to the following: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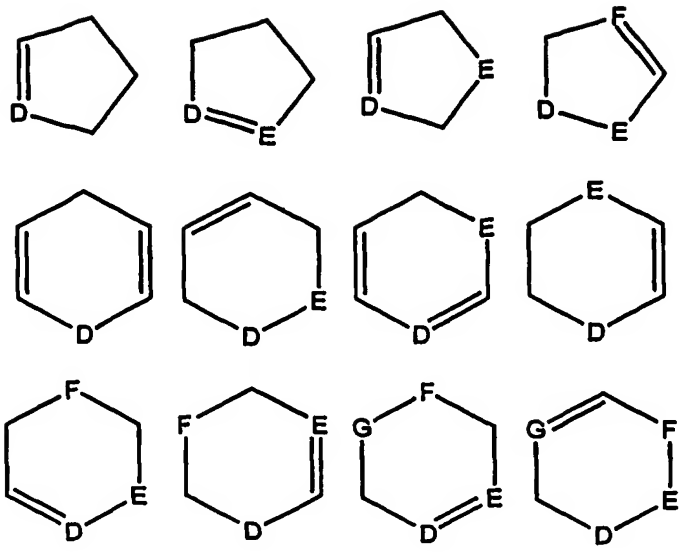


wherein D, E, F, and G each independently represent a heteroatom. Each of D, E, F, and G may be the same as or different from each other.

[037] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, and phosphorus, but are not limited to those atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms may all be the same, or some or all of the two or more heteroatoms may each be different from the others.

[038] The term "aromatic" refers to a group comprising a covalently closed ring having a delocalized π-electron system. Aromatic rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics may be optionally substituted. Examples of aromatic groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. The term aromatic includes, for example, benzenoid groups, connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from an aryl, a

heteroaryl, a cycloalkyl, a non-aromatic heterocycle, a halo, a hydroxy, an amino, a cyano, a nitro, an alkylamido, an acyl, a C_{1-6} alkoxy, a C_{1-6} alkyl, a C_{1-6} hydroxyalkyl, a C_{1-6} aminoalkyl, a C_{1-6} alkylamino, an alkylsulfenyl, an alkylsulfinyl, an alkylsulfonyl, an sulfamoyl, anda trifluoromethyl. In certain embodiments, an aromatic group is substituted at one or more of the para, meta, and/or ortho positions. Examples of aromatic groups comprising substitutions include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, (trifluoromethyl)phenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[039] The term "aryl" refers to an aromatic group wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups may be optionally substituted.

[040] The term "heteroaryl" refers to an aromatic group wherein at least one atom forming the aromatic ring is a heteroatom. Heteroaryl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heteroaryl groups may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C_{3-8} heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In certain embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected

from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, and trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O-C_1-$_6$ alkyl, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, or amino-C_1-C_6 alkyl.

[041] The term "non-aromatic ring" refers to a group comprising a covalently closed ring that does not have a delocalized π-electron system.

[042] The term "cycloalkyl", alone or in combination, refers to a monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has from 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.Cycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Cycloalkyls may be optionally substituted.

[043] The term "non-aromatic heterocycle" refers to a group comprising a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. Non-aromatic heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Non-aromatic heterocycles may be optionally substituted. In

certain embodiments, non-aromatic heterocycles comprise one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of non-aromatic heterocycles include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane.

[044] The term "arylalkyl" refers to a group comprising an aryl group bound to an alkyl group.

[045] The term "carbocycloalkyl" refers to a group comprising a carbocyclic cycloalkyl ring. Carbocycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycloalkyl groups may be optionally substituted.

[046] The term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryls and non-aromatic heterocycles), aromatics (*e.g.*, aryls and heteroaryls), and non-aromatics (*e.g.*, cycloalkyls and non-aromatic heterocycles). Rings may be optionally substituted. Rings may form part of a ring system.

[047] The term "ring system" refers to two or more rings, wherein two or more of the rings are fused. The term "fused" refers to structures in which two or more rings share one or more bonds.

[048] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[049] The term "null" refers to a group being absent from a structure. For example, in the structure  , if X is C, then both R' and R" exist, but if X is N, then one of those R groups is null, meaning that only three groups are bound to the N.

[050] The term "O-carboxy" refers to a group of formula RC(=O)O-.

[051] The term "C-carboxy" refers to a group of formula -C(=O)OR.

[052] The term "acetyl" refers to a group of formula $-C(=O)CH_3$.

[053] The term "trihalomethanesulfonyl" refers to a group of formula X3CS(=O)2- where X is a halogen.

[054] The term "cyano" refers to a group of formula -CN.

[055] The term "isocyanato" refers to a group of formula -NCO.

[056] The term "thiocyanato" refers to a group of formula -CNS.

[057] The term "isothiocyanato" refers to a group of formula -NCS.

[058] The term "sulfonyl" refers to a group of formula -S(=O)-R.

[059] The term "S-sulfonamido" refers to a group of formula $-S(=O)_2NR$.

[060] The term "N-sulfonamido" refers to a group of formula $RS(=O)_2NH-$.

[061] The term "trihalomethanesulfonamido" refers to a group of formula $X_3CS(=O)_2NR$-.

[062] The term "O-carbamyl" refers to a group of formula -OC(=O)-NR.

[063] The term "N-carbamyl" refers to a group of formula ROC(=O)NH-.

[064] The term "O-thiocarbamyl" refers to a group of formula -OC(=S)-NR.

[065] The term "N-thiocarbamyl" refers to a group of formula ROC(=S)NH-.

[066] The term "C-amido" refers to a group of formula $-C(=O)-NR_2$.

[067] The term "N-amido" refers to a group of formula RC(=O)NH-.

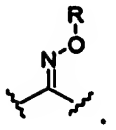
[068] The term "ester" refers to a chemical moiety with formula $-(R)_n$-COOR', where R and R' are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon), where n is 0 or 1.

[069] The term "amide" refers to a chemical moiety with formula -(R)n-C(O)NHR' or -(R)n-NHC(O)R', where R and R' are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), where n is 0 or 1. In certain embodiments, an amide may be an amino acid or a peptide.

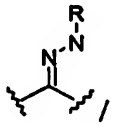
[070] The term "alkoxy," refers to an alkyl ether radical. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

[071] The term "formyl" includes aldehydes attached to a compound via an alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl group (*e.g.*, -alkyl-CHO, -aryl-CHO, -arylalkyl-CHO or –heteroarylalkyl-CHO, etc.).

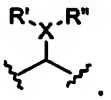
[072] The term "oxime" refers to a group of formula:



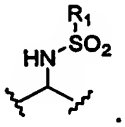
[073] The term "hydrazone" refers to a group of formula:



[074] The term "hydroxylamine" refers to a group of formula:



[075] The term sulfonamide refers to a group of formula:



[076] The term "halogen" includes F, Cl, Br and I

[077] The terms "amine," "hydroxy," and "carboxyl" include such groups that have been esterified or amidified. Procedures and specific groups used to achieve esterification and amidification are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic

Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated by reference herein in its entirety.

[078] Unless otherwise indicated, the term "optionally substituted," refers to a group in which none, one, or more than one of the hydrogen atoms has been replaced with one or more group(s) individually and independently selected from: alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heterohaloalkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, alkenylthio, alkynylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives of amino groups. Such protective derivatives (and protecting groups that may form such protective derivatives) are known to those of skill in the art and may be found in references such as Greene and Wuts, above. In embodiments in which two or more hydrogen atoms have been substituted, the substituent groups may together form a ring.

[079] The term "carrier" refers to a compound that facilitates the incorporation of another compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly used carrier for improving incorporation of certain organic compounds into cells or tissues.

[080] The term "pharmaceutical agent" refers to a chemical compound or composition capable of inducing a desired therapeutic effect in a patient. In certain embodiments, a pharmaceutical agent comprises an active agent, which is the agent that

induces the desired therapeutic effect. In certain embodiments, a pharmaceutical agent comprises a prodrug. In certain embodiments, a pharmaceutical agent comprises inactive ingredients such as carriers, excipients, and the like.

[081] The term "therapeutically effective amount" refers to an amount of a pharmaceutical agent sufficient to achieve a desired therapeutic effect.

[082] The term "prodrug" refers to a pharmaceutical agent that is converted from a less active form into a corresponding more active form *in vivo*.

[083] The term "pharmaceutically acceptable" refers to a formulation of a compound that does not significantly abrogate biological activity, a pharmacological activity and/or other properties of the compound when the formulated compound is administered to a patient. In certain embodiments, a pharmaceutically acceptable formulation does not cause significant irritation to a patient.

[084] The term "co-administer" refers to administering more than one pharmaceutical agent to a patient. In certain embodiments, co-administered pharmaceutical agents are administered together in a single dosage unit. In certain embodiments, co-administered pharmaceutical agents are administered separately. In certain embodiments, co-administered pharmaceutical agents are administered at the same time. In certain embodiments, co-administered pharmaceutical agents are administered at different times.

[085] The term "patient" includes human and animal subjects.

[086] The term "substantially pure" means an object species (*e.g.*, compound) is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially purified pure composition is a composition wherein the object species comprises at least about 50

percent (on a molar basis) of all species present. In certain embodiments, a substantially pure composition is a composition wherein the object species comprises more than about 80%, 85%, 90%, 95%, or 99% of all species present in the composition. In certain embodiments, a substantially pure object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of the single object species.

[087] The term "tissue-selective" refers to the ability of a compound to modulate a biological activity in one tissue to a greater or lesser degree than it modulates a biological activity in another tissue. The biological activities modulated in the different tissues may be the same or they may be different. The biological activities modulated in the different tissues may be mediated by the same type of target receptor. For example, in certain embodiments, a tissue-selective compound may modulate an HNF-4α receptor-mediated biological activity in one tissue and fail to modulate, or modulate to a lesser degree, an HNF-4α receptor-mediated biological activity in another tissue type.

[088] The term "monitoring" refers to observing an effect or absence of any effect. In certain embodiments, cells are monitored after contacting those cells with a compound of the present invention. Examples of effects that may be monitored include, but are not limited to, changes in cell phenotype, cell proliferation, an HNF-4α receptor activity, or the interaction between an HNF-4α receptor and a natural binding partner.

[089] The term "cell phenotype" refers to physical or biological characteristics. Examples of characteristics that constitute phenotype included, but are not limited to, cell size, cell proliferation, cell differentiation, cell survival, apoptosis (cell death), or the

utilization of a metabolic nutrient (*e.g.*, glucose uptake). Certain changes or the absence of changes in cell phenotype are readily monitored using techniques known in the art.

[090] The term "cell proliferation" refers to the rate at which cells divide. The number of cells growing in a vessel can be quantified by a person skilled in the art (*e.g.*, by counting cells in a defined area using a light microscope, or by using laboratory apparatus that measure the density of cells in an appropriate medium). One skilled in that art can calculate cell proliferation by determining the number of cells in a sample at two or more times.

[091] The term "contacting" refers to bringing two or more materials into close enough proximity that they may interact. In certain embodiments, contacting can be accomplished in a vessel such as a test tube, a petri dish, or the like. In certain embodiments, contacting may be performed in the presence of additional materials. In certain embodiments, contacting may be performed in the presence of cells. In certain of such embodiments, one or more of the materials that are being contacted may be inside a cell. Cells may be alive or may dead. Cells may or may not be intact.

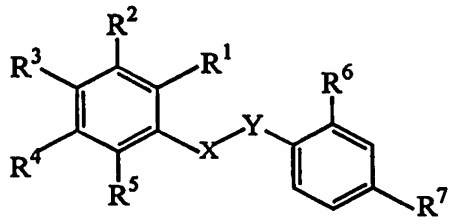
Certain compounds

[092] Certain compounds that bind to HNF-4α receptors and/or certain compounds that modulate an activity of such receptors play a role in health (*e.g.*, normal growth, development, and/or absence of disease). In certain embodiments, compounds of the present invention are useful for treating any of a variety of diseases or conditions.

[093] Certain compounds have been previously described as receptor modulators. See *e.g.*, U. S. Patent Nos. 6,462,038, 5,693,646; 6,380,207; 6,506,766; 5,688,810; 5,696,133; 6,569,896, 6,673,799; 4,636,505; 4,097,578; 3,847,988; U.S. Pat Application No. 10/209,461 (Pub. No. US 2003/0055094); International Patent

Application Nos. WO 01/27086 &WO 02/22585; Zhi, *et al. Bioorganic & Med. Chem. Lett.* (2000) 10:415-418; Pooley, *et al., J. Med. Chem.* (1998) 41:3461; Hamann, *et al. J. Med. Chem.* (1998) 41:623; and Yin, *et al., Molec. Pharmacol.* (2003) 63:211-223 the entire disclosures of which are incorporated by reference herein in their entirety. Certain cyclothiocarbamate analogues have been described as progesterone receptor modulators (*e.g.*, US 6,436,929 and US 6,509,334). Certain cyclocarbamate analogues have been described as progesterone receptor antagonists (*e.g.*, U.S. Pat. Nos. 6,306,851, 6,380,178, 6,441,019, 6,444,668, 6,509,334, and 6,566,358; Zhang, *et al. J. Med. Chem.* 45:4379 (2002)).

[094] In certain embodiments, the invention provides a compound of formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

[095] In certain embodiments, R^1 is selected from H, a halogen, a C_1–C_6 alkyl optionally substituted with one or more halogens,a C_2-C_6 alkenyl optionally substituted with one or more halogens, a C_2-C_6 alkynyl optionally substituted with one or more halogens, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted

C_2-C_6 haloalkynyl, an optionally substituted C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heterohaloalkenyl, an optionally substituted C_2-C_6 heterohaloalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, an optionally substituted C_1-C_2 alkoxy, an optionally substituted sulfonamide, an optionally substituted C_1-C_2 thioalkyl, an optionally substituted C_2 thoalkenyl, an optionally substituted C_2 thioalkynyl, an optionally substituted nitro, an optionally substituted formyl, an optionally substituted acyl, and an optionally substituted hydroxylamine. In certain embodiments, R^1 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^1 is an optionally substituted C_1-C_8 alkyl an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl,, an optionally substituted C_2-C_8 heteroalkyl an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^1 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 heteroalkenyl, an optionally substituted C_2-C_3 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^1 is selected from an optionally substituted

methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^1 is a halogen, R^1 is F or Cl.

[096] In certain embodiments, R^2 and R^4 are each independently selected from H, a halogen, a C_1-C_3 alkoxy optionally substituted with one or more halogens, a carbocyclic or heterocyclic ring optionally substituted with one or more halogens, a nitro, $NR^{13}R^{14}$, a C_1–C_6 alkyl substituted with one or more halogens, a C_2-C_6 alkenyl substituted with one or more halogens, a C_2-C_6 alkynyl optionally substituted with one or more halogens, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloalkynyl, an optionally substituted C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heterohaloalkenyl, an optionally substituted C_2-C_6 heterohaloalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, an optionally substituted sulfonamide, an optionally substituted C_1-C_2 thioalkyl, an optionally substituted C_2 thioalkenyl, an optionally substituted C_2 thioalkynyl, an optionally substituted nitro, an optionally substituted formyl, an optionally substituted acyl, and an optionally substituted hydroxylamine. In certain embodiments, R^2 and/or R^4 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8

cycloalkynyl. In certain embodiments, R^2 and/or R^4 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^2 and/or R^4 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 heteroalkenyl, an optionally substituted C_2-C_3 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^2 and/or R^4 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^2 and/or R^4 is a halogen, R^2 and/or R^4 is F or Cl.

[097] In certain embodiments, R^1 and R^2 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}. Thus, the ring formed by R^1 and R^2 in such embodiments would share a bond with the ring to which R^1 and R^2 are both bound.

[098] In certain embodiments, R^3 is selected from H, a halogen, an acyl, a methyl optionally substituted with one or more halogens, and a methoxy optionally substituted with one or more halogens.

[099] In certain embodiments, R^2 and R^3 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}. Thus, the ring formed by R^2 and R^3 in such embodiments would share a bond with the ring to which R^2 and R^3 are both bound.

[0100] In certain embodiments, R^3 and R^4 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}. Thus, the ring formed by R^3 and R^4 in such embodiments would share a bond with the ring to which R^3 and R^4 are both bound.

[0101] In certain embodiments, R^5 is selected from H, a halogen, a C_1-C_6 alkyl optionally substituted with one or more halogens, a C_2-C_6 alkenyl optionally substituted with one or more halogens, C_2-C_6 alkynyl optionally substituted with one or more halogens, a C_1-C_5 alkoxy optionally substituted with one or more halogens, a C_1-C_5 thioalkyl optionally substituted with one or more halogens, a C_2-C_5 thioalkenyl optionally substituted with one or more halogens, a C_2-C_5 thioalkynyl optionally substituted with one or more halogens, a carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}, an acyl, a nitro, and $NR^{16}R^{17}$. In certain embodiments, $R^5$is an optionally substituted C_1-C_5 alkyl, an optionally substituted C_2-C_5 alkenyl, an optionally substituted C_2-C_5 alkynyl,, an optionally substituted C_1-C_5 heteroalkyl, an optionally substituted C_2-C_5 heteroalkenyl, an optionally substituted C_2-C_5 heteroalkynyl,, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, $R^5$is an optionally substituted C_1-C_5 alkyl, an optionally substituted C_2-C_5 alkenyl, an optionally substituted C_2-C_5 alkynyl, an optionally substituted C_1-C_5 heteroalkyl an optionally substituted C_2-C_5 heteroalkenyl, an optionally substituted C_2-C_5 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^5 is selected from an optionally substituted C_2-C_5 alkenyl, an optionally substituted C_2-C_5 alkynyl, an optionally substituted C_2-C_5 heteroalkenyl, an optionally

substituted C_2-C_5 heteroalkynyl, an optionally substituted C_3-C_8 heteroalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^5 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where $R^5$is a halogen, $R^5$is F or Cl.

[0102] In certain embodiments, R^4 and R^5 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{15}. Thus, the ring formed by R^4 and R^5 in such embodiments would share a bond with the ring to which R^4 and R^5 are both bound.

[0103] In certain embodiments, R^6 is selected from H, a halogen, a methyl optionally substituted with one or more fluorines and a methoxy.

[0104] In certain embodiments, R^7 is selected from an optionally CH_2OH, CHO, a carboxylic acid or a pharmaceutically acceptable salt thereof, $C(R^9)(R^{10})CO_2H$ or a pharmaceutically acceptable salt thereof, $(C(R^9)(R^{10}))_nCO_2(CH_2)_mCH_3$, $O(C(R^9)(R^{10}))_nCO_2H$, $O(C(R^9)(R^{10}))_nCO_2(CH_2)_mCH_3$, an optionally substituted C_1–C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloalkynyl, an optionally substituted C_1-C_6 heterohaloalkyl, C_2-C_6 heterohaloalkenyl, C_2-C_6 heterohaloalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, and an optionally substituted C_1-C_2 alkoxy. In certain embodiments, R^7 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8

alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^7 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, or an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^7 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 heteroalkenyl, an optionally substituted C_2-C_3 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl.

[0105] In certain embodiments, m and n are each independently selected from 0, 1, 2, and 3.

[0106] In certain embodiments, R^9 and R^{10} are each independently selected from H, F, and OH. In certain embodiments, R^9 and R^{10} taken together form an oxygen.

[0107] In certain embodiments, R^{13} and R^{14} are each independently selected from H, a carbocyclic ring optionally substituted with one or more halogens, C_1–C_6 alkyl substituted with one or more halogens, C_2-C_6 alkenyl substituted with one or more halogens, C_2-C_6 alkynyl substituted with one or more halogens, an optionally substituted C_1-C_6 heteroalkyl an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloalkynyl, an optionally substituted

C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heterohaloalkenyl, an optionally substituted C_2-C_6 heterohaloalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, and an optionally substituted C_1-C_2 alkoxy. In certain embodiments, R^{13} and/or R^{14} is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^{13} and/or R^{14} is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl,, an optionally substituted C_2-C_8 heteroalkyl an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^{13} and/or R^{14} is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 heteroalkenyl, an optionally substituted C_2-C_3 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^{13} and/or R^{14} is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^{13} and/or R^{14} is a halogen, R^1 is F or Cl.

[0108] In certain embodiments R^{13} and R^{14} taken together with the nitrogen to which they are each bound to form a five to eight-membered heterocyclic ring.

[0109] In certain embodiments, R^{15} is selected from H, a halogen, NO_2, a cyano, an acyl, a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, a C_2-C_3 alkynyl optionally substituted with one or more halogens, a C_1-C_2 alkoxy optionally substituted with one or more halogens, C_1-C_2 thioalkyl optionally substituted with one or more halogens, a C_2 thioalkenyl optionally substituted with one or more halogens, and a C_2 thioalkynyl optionally substituted with one or more halogens.

[0110] In certain embodiments, R^{16} and R^{17} are each independently selected from H, a C_1-C_5 alkyl optionally substituted with one or more halogens, C_2-C_5 alkenyl optionally substituted with one or more halogens, C_2-C_5 alkynyl optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more R^{15}; and

[0111] In certain embodiments, X and Y are each independently selected from a methylene optionally substituted with an oxime or with one or more halogens, a C_1-C_2 alkyl, optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, a C_2-C_6 alkynyl optionally substituted with one or more halogens, O, S, NR^{18}, and benzyl optionally substituted with one or more fluorines. In certain embodiments, X and/or Y is a carbonyl. In certain embodiments, X is a carbonyl. In certain embodiment, X and Y together form and olefin.

[0112] In certain embodiments, if X is methylene, then Y is selected from NR^{18}, O and S; if Y is methylene, then X is selected from NR^{18}, O and S; and R^{18} is selected from H a C_1-C_5 alkyl, a C_2-C_5 alkenyl, and a C_2-C_5 alkynyl.

[0113] In embodiments in which two or more of a particular group are present, the identities of those two or more particular groups are selected independently and, thus,

may be the same or different from one another. For example, certain compounds of the invention comprise two or more R^{15} groups. The identities of those two or more R^{15} groups are each selected independently. Thus, in certain embodiments, those R^{15} groups are all the same as one another; in certain embodiments, those R^{15} groups are all different from one another; and in certain embodiments, some of those R^{15} groups are the same as one another and some are different from one another. This independent selection applies to any group that is present in a compound more than once.

[0114] Certain compounds of the present inventions may exist as stereoisomers including, but not limited to, optical isomers. The present disclosure is intended to include all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are known in the art or that may be excluded by synthesis schemes known in the art designed to yield predominantly one enantomer relative to another.

[0115] As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers." The terms "racemate," "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

[0116] The compounds of the present invention may be chiral, and it is intended that any enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention. Furthermore, when a double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention. Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention. Thus, as one skilled in the art knows, certain aryls may exist in tautomeric forms. The invention also includes tautomers, enantiomers and other stereoisomers of the compounds of Formula I. Such variations are contemplated to be within the scope of the invention.

[0117] The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

[0118] The designation " " refers to a bond that protrudes forward out of the plane of the page.

[0119] The designation " " refers to a bond that protrudes backward out of the plane of the page.

[0120] The designation " " refers to a bond wherein the stereochemistry is not defined.

[0121] The compounds of Formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration or through enantioselective synthesis.

[0122] The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee," which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

[0123] wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first enantiomer is 40%.

However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the specific stereoisomers and enantiomers of compounds of Formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions," John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds," (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

[0124] The following table provides examples of certain variables from various Markush groups in this application. One of ordinary skill in the art will recognize that the variables may selected in any combination.

Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_1	H, halogen, and C_1-C_4 alkyl optionally substituted with one or more halogens	H or halogen	C_1-C_4 alkyl optionally substituted with one or more halogens	H
R_2	H, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_3 alkoxy, a carbocyclic ring, a heterocyclic ring, nitro, and $NR_{13}R_{14}$, wherein said alkyl, alkenyl, alkoxy, carbocyclic and heterocyclic groups are optionally substituted with one or more halogens; or R_1 and R_2 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15}; or R_2 and R_3 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15};	H, halogen, C_2-C_4 alkyl, C_2-C_4 alkenyl, and C_2-C_3 alkoxy, wherein said alkyl, alkenyl and alkoxy, groups are optionally substituted with one or more halogens;	a carbocyclic ring, a heterocyclic ring, nitro, and $NR_{13}R_{14}$, wherein said carbocyclic and heterocyclic groups are optionally substituted with one or more halogens;	H, halogen, C_1-C_2 alkyl, C_2 alkenyl, and C_1-C_2 alkoxy, wherein the alkyl, alkenyl and alkoxy groups are optionally substituted with one or more halogens;

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_3	H, halogen, acyl, a methyl group optionally substituted with one or more halogens, a methoxy group optionally substituted with one or more halogens; or R_2 and R_3 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15}; or R_3 and R_4 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15};	H, halogen, and acyl;	H, methyl group optionally substituted with one or more halogens, a methoxy group optionally substituted with one or more halogens;	H and halogen;

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_4	H, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_3 alkoxy, a carbocyclic ring, a heterocyclic ring, nitro, and $NR_{13}R_{14}$, wherein said alkyl, alkenyl, alkoxy, carbocyclic and heterocyclic groups are optionally substituted with one or more halogens; or R_3 and R_4 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15}; or R_4 and R_5 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15};	H, halogen, C_2-C_4 alkyl, C_2-C_4 alkenyl, and C_2-C_3 alkoxy, wherein said alkyl, alkenyl and alkoxy, groups are optionally substituted with one or more halogens;	a carbocyclic ring, a heterocyclic ring, nitro, and $NR_{13}R_{14}$, wherein said carbocyclic and heterocyclic groups are optionally substituted with one or more halogens;	H, halogen, C_1-C_2 alkyl, C_2 alkenyl, and C_1-C_2 alkoxy; wherein the alkyl, alkenyl and alkoxy groups are optionally substituted with one or more halogens;

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_5	H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_5 alkoxy, C_1-C_5 thioalkyl, C_2-C_5 thioalkenyl, C_2-C_5 thioalkynyl, a carbocyclic or heterocyclic ring optionally substituted with one or more R_{15}, acyl, nitro, and $NR_{16}R_{17}$, wherein said alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more halogens; or R_4 and R_5 taken together form a five to eight-membered carbocyclic or heterocyclic ring optionally substituted with one or more R_{15};	H, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, C_1-C_4 thioalkyl, C_2-C_4 thioalkenyl, C_2-C_4 thioalkynyl, wherein said alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more halogens	a carbocyclic or heterocyclic ring optionally substituted with one or more R_{15}, acyl, nitro, and $NR_{16}R_{17}$	H, halogen, C_2-C_4 alkyl, wherein said alkyl group is optionally substituted with one or more halogens
R_6	H, halogen, a methyl group optionally substituted with one or more fluorines or a methoxy group;	H, halogen, a methyl group optionally substituted with one or more fluorines;	H and a methoxy group;	H and halogen

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_7	CH_2OH, CHO, a carboxylic acid or a pharmaceutically acceptable salt thereof, $C(R_9)(R_{10})CO_2H$ or a pharmaceutically acceptable salt thereof;	CH_2OH, CHO, a carboxylic acid or a pharmaceutically acceptable salt thereof;	CH_2OH, CHO, $C(R_9)(R_{10})CO_2H$ or a pharmaceutically acceptable salt thereof;	CH_2OH and CHO
R_9	H, F and OH; or R_9 and R_{10} together form an oxygen	H and F;	H and OH	H
R_{10}	H, F and OH; or R_9 and R_{10} together form an oxygen	H and F;	H and OH	H
R_{13}	H, C_1-C_5 alkyl or C_2-C_5 alkenyl group optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more halogens; R_{13} and R_{14} taken together with the nitrogen to which they are each bound to form a five to eight-membered heterocyclic ring;	H, C_2-C_4 alkyl or C_2-C_4 alkenyl group optionally substituted with one or more halogens;	carbocyclic ring optionally substituted with one or more halogens;	H, C_2-C_3 alkyl or C_2-C_3 alkenyl group optionally substituted with one or more halogens;

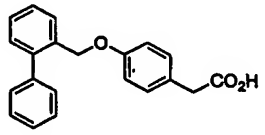
	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_{14}	H, C_1-C_5 alkyl or C_2-C_5 alkenyl group optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more halogens; or R_{13} and R_{14} taken together with the nitrogen to which they are each bound to form a five to eight-membered heterocyclic ring;	H, C_2-C_4 alkyl or C_2-C_4 alkenyl group optionally substituted with one or more halogens;	carbocyclic ring optionally substituted with one or more halogens;	H, C_2-C_3 alkyl or C_2-C_3 alkenyl group optionally substituted with one or more halogens;
R_{15}	H, halogen, NO_2, cyano, acyl, C_1-C_3 alkyl or C_2-C_3 alkenyl group optionally substituted with one or more halogens, C_1-C_2 alkoxy group optionally substituted with one or more halogens, and C_1-C_2 thioalkyl or C_2 thioalkenyl group optionally substituted with one or more halogens;	H, halogen, NO_2, cyano, acyl, C_1-C_2 alkyl or C_2 alkenyl group optionally substituted with one or more halogens, C_1-C_2 alkoxy group optionally substituted with one or more halogens;	H, halogen, C_1-C_2 alkyl optionally substituted with one or more halogens, C_1-C_2 alkoxy group optionally substituted with one or more halogens;	H and halogen

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_{16}	H, C_1-C_5 alkyl or C_2-C_5 alkenyl group optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more R_{15};	H, C_2-C_4 alkyl or C_2-C_4 alkenyl group optionally substituted with one or more halogens;	H, C_1-C_2 alkyl or C_2 alkenyl group optionally substituted with one or more halogens	H
R_{17}	H, C_1-C_5 alkyl or C_2-C_5 alkenyl group optionally substituted with one or more halogens, and a carbocyclic ring optionally substituted with one or more R_{15};	H, C_2-C_4 alkyl or C_2-C_4 alkenyl group optionally substituted with one or more halogens;	H, C_1-C_2 alkyl or C_2 alkenyl group optionally substituted with one or more halogens	H
R_{18}	H and C_1-C_5 alkyl;	H and C_2-C_4 alkyl;	H and C_1-C_2 alkyl;	H;
X	methylene optionally substituted with one or more halogens, C_1-C_2 alkyl optionally substituted with one or more halogens, oxygen, sulfur, NR_{18}, and benzyl optionally substituted with one or more fluorines; with the proviso that if X is methylene, then Y is NR_{18}, O or S, and if Y is methylene, then X is NR_{18}, O or S	methylene optionally substituted with one or more halogens, C_1-C_2 alkyl optionally substituted with one or more halogens, oxygen, sulfur, and NR_{18}, with the proviso that if X is methylene, then Y is NR_{18}, O or S, and if Y is methylene, then X is NR_{18}, O or S	oxygen and sulfur	

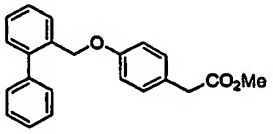
	Markush Group A	Markush Group B	Markush Group C	Markush Group D
Y	methylene optionally substituted with one or more halogens, C_1-C_2 alkyl optionally substituted with one or more halogens, oxygen, sulfur, NR_{18}, and benzyl optionally substituted with one or more fluorines; with the proviso that if X is methylene, then Y is NR_{18}, O or S, and if Y is methylene, then X is NR_{18}, O or S	methylene optionally substituted with one or more halogens, C_1-C_2 alkyl optionally substituted with one or more halogens, oxygen, sulfur, and NR_{18}, with the proviso that if X is methylene, then Y is NR_{18}, O or S, and if Y is methylene, then X is NR_{18}, O or S	oxygen and sulfur	

In certain embodiments, the invention provides compounds selected from:

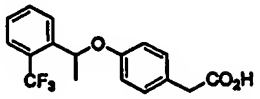
4-(2-phenylbenzyloxy)phenylacetic acid (Compound 1)



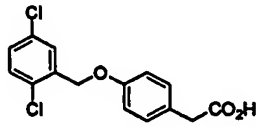
Methyl-4-(2-phenylbenzyloxy)phenylacetate (Compound 2)



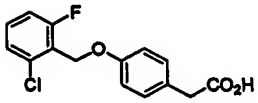
4-[(2-trifluoromethyl)-α-methyl benzyloxy]phenyl acetic acid (Compound 3)



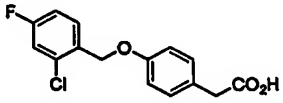
4-(2,5-dichlorobenzyloxy)phenyl acetic acid (Compound 4)



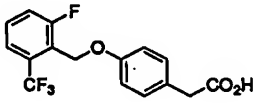
4-(2-chloro-6-fluorobenzyloxy)phenyl acetic acid (Compound 5)



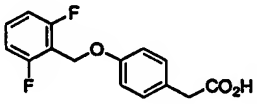
4-(2-chloro-4-fluorobenzyloxy)phenyl acetic acid (Compound 6)



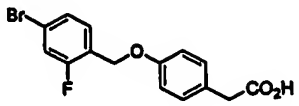
4-(2-fluoro-6-trifluoromethylbenzyloxy) phenyl acetic acid (Compound 7)



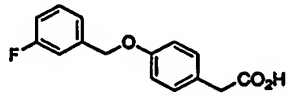
4-(2,6-difluorobenzyloxy)phenyl acetic acid (Compound 8)



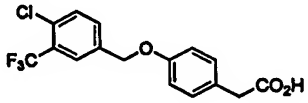
4-(2-fluoro-4-bromobenzyloxy)phenyl acetic acid (Compound 9)



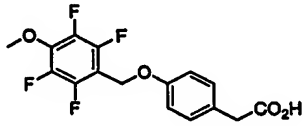
4-(3-fluorobenzyloxy)phenyl acetic acid (Compound 10)



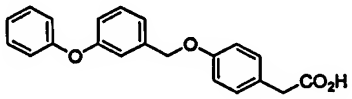
4-(4-chloro-3-trifluoromethylbenzyloxy)phenyl acetic acid (Compound 11)



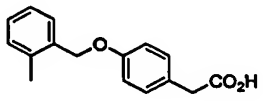
4-(1,2,5,6-tetrafluoro-4-methoxybenzyloxy)phenyl acetic acid (Compound 12)



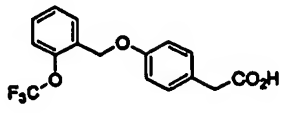
4-(3-phenoxybenzyloxy)phenyl acetic acid (Compound 13)



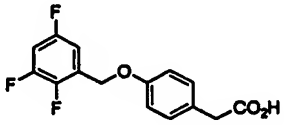
4-(2-methylbenzyloxy)phenyl acetic acid (Compound 14)



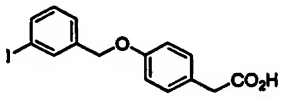
4-(2-trifluoromethoxybenzyloxy)phenylacetic acid (Compound 15)



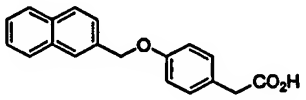
4-(2,3,5-trifluorobenzyloxy)phenylacetic acid (Compound 16)



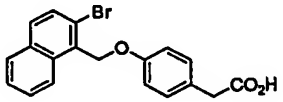
4-(3-iodobenzyloxy)phenylacetic acid (Compound 17)



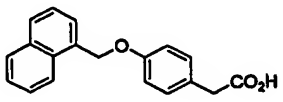
4-(2-naphthalenoxy)phenyl acetic acid (Compound 18)



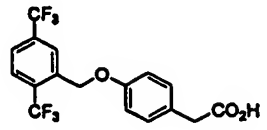
4-[1-(2-bromo)naphthalenoxy]phenylacetic acid (Compound 19)



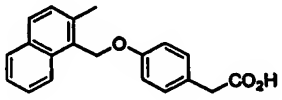
4-(1-naphthalenoxy)phenylacetic acid (Compound 20)



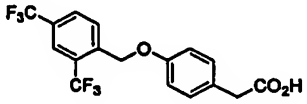
4-(2,5-bistrifluoromethylbenzyloxy)phenyl acetic acid (Compound 21)



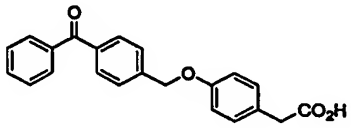
4-[1-(2-methyl)naphthalenoxy]phenylacetic acid (Compound 22)



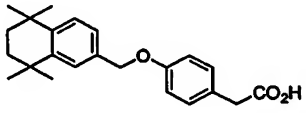
4-(2,4-bistrifluoromethylbenzyloxy)phenylacetic acid (Compound 23)



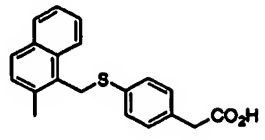
4-(4-benzoylbenzyloxy)phenylacetic acid (Compound 24)



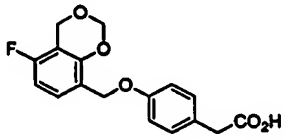
4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthyloxy)] phenylacetic acid (Compound 25)



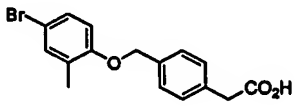
4-[1-(2-methyl)naphthalenemethanethiol]phenyl acetic acid (Compound 26)



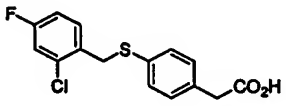
4-(4-fluoro-2,3-bezo-1,3-dioxanyloxy)phenylacetic acid (Compound 27)



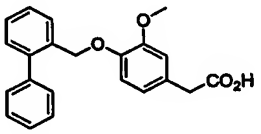
4-(2-methyl-4-bromobenzyloxy)phenylacetic acid (Compound 28)



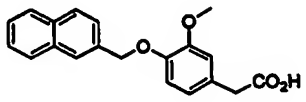
4-(2-chloro-4-fluorobenzylmercapto)phenylacetic acid (Compound 29)



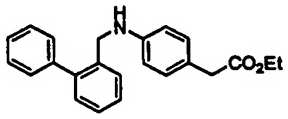
3-methoxy-4-(2-phenylbenzyloxy)phenylacetic acid (Compound 30)



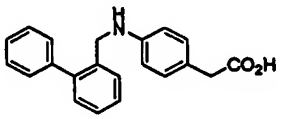
3-methoxy-4-(2-naphthalenoxy)phenylacetic acid (Compound 31)



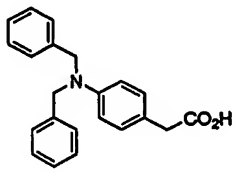
Ethyl-4-(2-phenyl)benzylamino phenyl acetic acid (Compound 32)



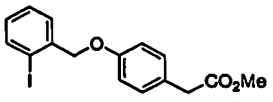
4-(2-phenyl)benzylamino phenyl acetic acid (Compound 33)



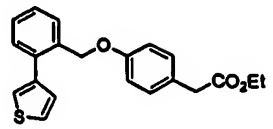
4-(*N*,*N*-dibenzylamino)phenylacetic acid (Compound 34)



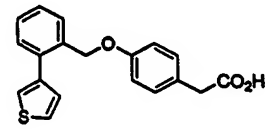
Methyl-4-(2-iodobenzyloxy)phenyl acetate (Compound 35)



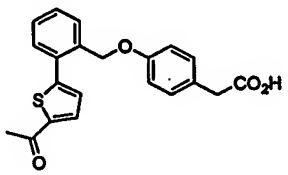
Ethyl-4-(2-(3-thienyl)benzyloxy)phenyl acetate (Compound 36)



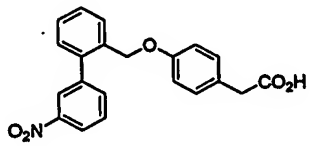
4-(2-(3-thienyl)benzyloxy)phenyl acetic acid (Compound 37)



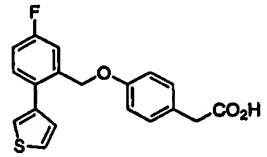
4-[2-(5-acetyl-2-thienyl)]benzyloxy phenylacetic acid (Compound 38)



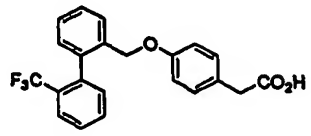
4-[2-(3-nitro)phenylbenzyloxy]phenyl acetic acid (Compound 39)



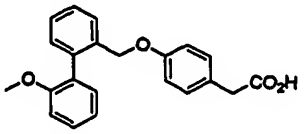
4-[2-(3-thienyl)-5-fluorobenzyl]phenyl acetic acid (Compound 40)



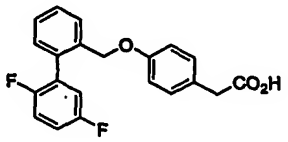
4-[2-(2-trifluoromethyl)phenylbenzyloxy]phenyl acetic acid (Compound 41)



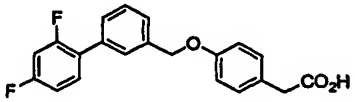
4-[2-(2-methoxy)phenylbenzyloxy]phenyl acetic acid (Compound 42)



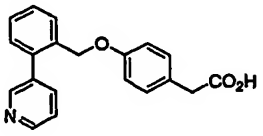
4-[2-(2,5-difluorophenyl)benzyloxy]phenylacetic acid (Compound 43)



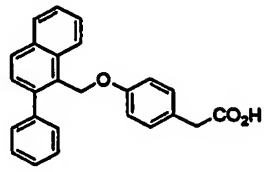
4-[3-(2,4-difluorophenyl)benzyloxy]phenylacetic acid (Compound 44)



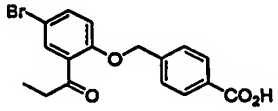
4-(3-pyridylbenzyloxy)phenylacetic acid (Compound 45)



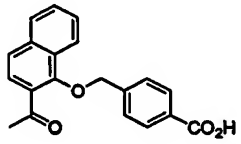
4-[1-(2-phenyl)naphthalenoxy]phenylacetic acid (Compound 46)



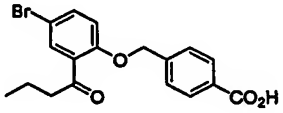
4-{[4-bromo-(2-propan-1-one)]phenyloxy}methyl benzoic acid (Compound 47)



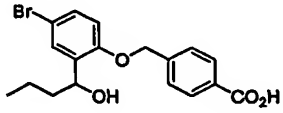
4-(2-acetyl-1-naphthyloxy)methyl benzoic acid (Compound 48)



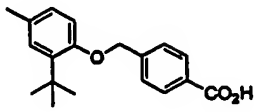
4-{[4-bromo-(2-butan-1-one)]phenyloxy}methyl benzoic acid (Compound 49)



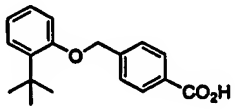
4-{[4-bromo-(2-butan-1-ol)]phenyloxy}methylbenzoic acid (Compound 50)



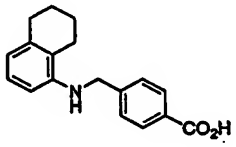
4-(2-*tert*-butyl-4-methylphenyl)phenyloxymethyl benzoic acid (Compound 51)



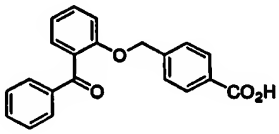
4-(2-*tert*-butylphenyloxy)methyl benzoic acid (Compound 52)



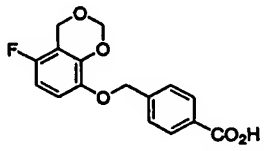
4-(5,6,7,8-tetrahydro-1-naphthylamino)methyl benzoic acid (Compound 53)



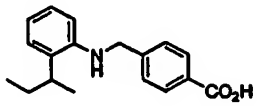
4-(2-benzoylphenyloxy)methyl benzoic acid (Compound 54)



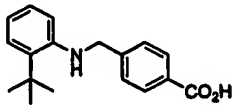
4-[4-fluoro-(2,3'-methylenedioxy)methyl]methyl benzoic acid (Compound 55)



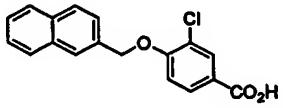
4-[2-(1-methylpropyl)phenylamino]methyl benzoic acid (Compound 56)



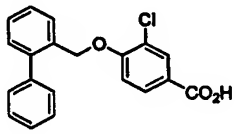
4-(2-*tert*-butylphenylamino)methyl benzoic acid (Compound 57)



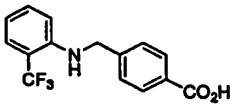
3-chloro-4-(2-naphthylmethoxy)benzoic acid (Compound 58)



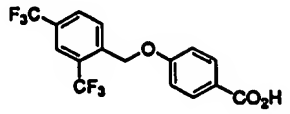
3-chloro-4-(2-phenylbenzyl)benzoic acid (Compound 59)



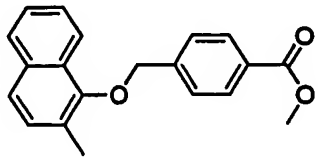
4-(2-trifluoromethylanilinomethyl)benzoic acid (Compound 60)



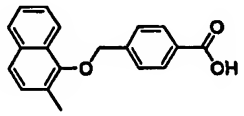
4-(2,4-bistrifluoromethylbenzyloxy)benzoic acid (Compound 61)



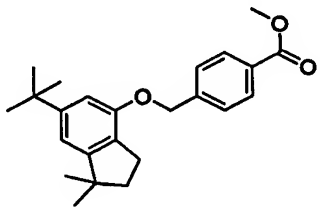
Methyl-4-(2-methyl-1-naphthyloxymethyl)benzoate (Compound 62)



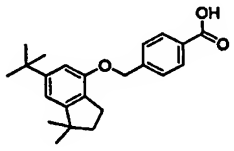
4-[(2-methyl-1-naphthyloxy)methyl]benzoic acid (Compound 63)



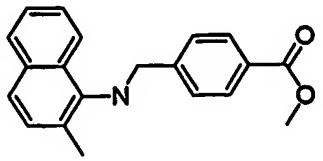
Methyl-4-(3-tert-butyl-5,5-dimethylindanoxymethyl)benzoate (Compound 64)



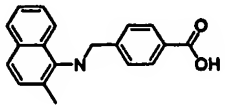
4-[(3-*tert*-butyl-5,5-dimethylindanoxy)methyl]benzoic acid (Compound 65)



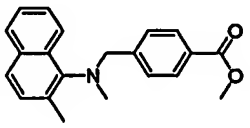
Methyl-4-(2-methyl-1-aminonaphylaminomethyl)benzoate (Compound 67)



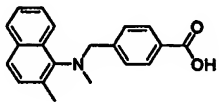
4-[(2-methyl-1-naphthylamino)methyl]benzoic acid (Compound 68)



Methyl-4-(2-methyl-1-N-ethylaminonaphylaminomethyl)benzoate (Compound 69)



N-methyl-4-[(2-methyl-1-naphthylamino)methyl]benzoic acid (Compound 70)



and pharmaceutically acceptable salts, esters, amides, and/or prodrugs of any of those compounds.

[0125] In certain embodiments, a compound of Formula I is a selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor agonist. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor antagonist. In certain embodiments, a compound of Formula

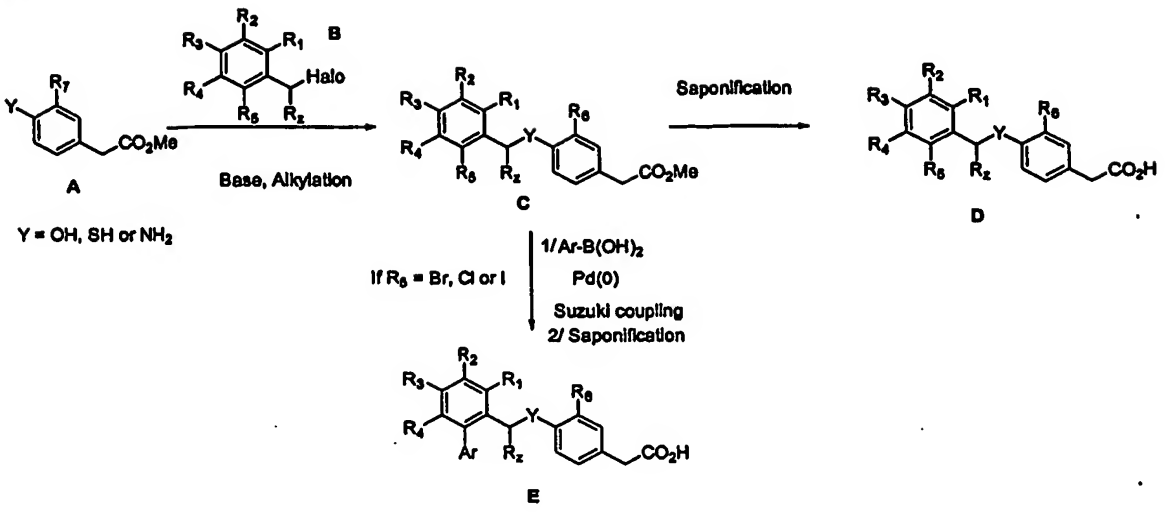
I is a selective HNF-4α receptor partial agonist. In certain embodiments, a compound of Formula I is a tissue-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a gene-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor binding compound.

[0126] In certain embodiments, the present invention provides selective HNF-4α receptor modulators. In certain embodiments, the invention provides selective HNF-4α receptor binding agents. In certain embodiments, the invention provides methods of making and methods of using selective HNF-4α receptor modulators and/or selective HNF-4α binding agents. In certain embodiments, selective HNF-4α modulators are agonists, partial agonists, and/or antagonists for the HNF-4α receptor. In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to a retinoic X receptor (RXR). In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to an RXR by at least 8 times.

Certain Synthesis Methods

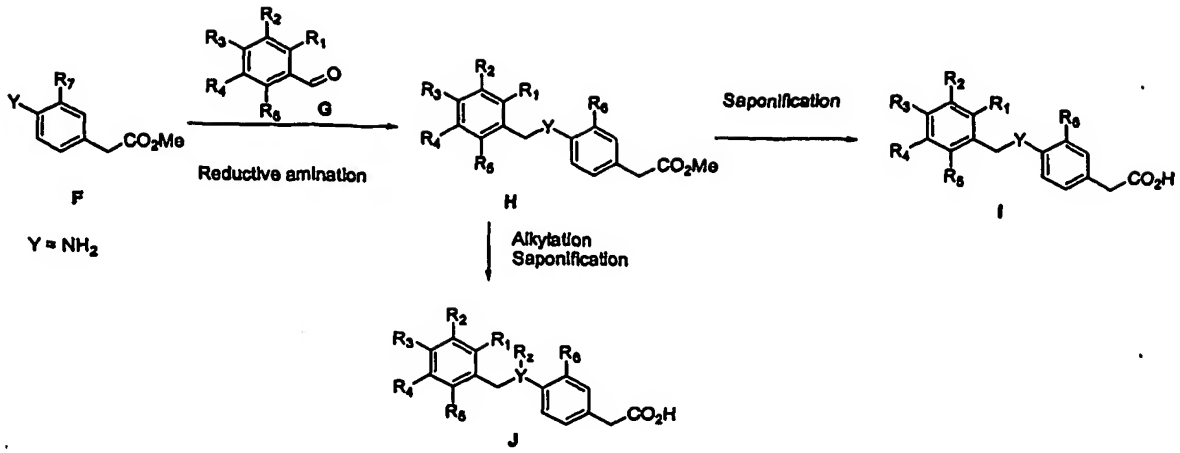
Compounds of formula I may be synthesized using the procedure described in schemes 1 and 2.

Scheme 1



Alkylation of derivatives **A** with various compounds **B** in the presence of base afford the esters **C** that release the acids **D** after saponification. Various substituents may be introduced using transition metal catalysis on **B** when this one possess a halogen (Cl, Br or I) on the benzyl phenyl ring. Saponification of these derivatives releases the acids **E**. Scheme 2 describes an alternate way of synthesizing compounds **I** and **J** (Y = N) via reductive amination of **F** with **G**.

Scheme 2



[0127] In certain embodiments, the invention provides a salt corresponding to any of the compounds provided herein. In certain embodiments, the invention provides a salt corresponding to a selective HNF-4α modulator. In certain embodiments, the invention provides a salt corresponding to a selective HNF-4α receptor binding agent. In certain embodiments, a salt is obtained by reacting a compound with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In certain embodiments, a salt is obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0128] In certain embodiments, one or more carbon atoms of a compound of the present invention is replaced with silicon. *See e.g.*, WO 03/037905A1; Tacke and Zilch, Endeavour, New Series, 10, 191-197 (1986); Bains and Tacke, Curr. Opin. Drug Discov Devel. Jul:6(4):526-43(2003). In certain embodiments, compounds of the present invention comprising one or more silicon atoms possess certain desired properties, including, but not limited to, greater stability and/or longer half-life in a patient, when compared to the same compound in which none of the carbon atoms have been replaced with a silicon atom.

[0129] Protecting groups that may be used in the present invention include those that are commonly known to those skilled in the art, such groups include, but are not limited to TBDMS, TBS and Benzyl.

Certain Assays

[0130] In certain embodiments, compounds of the present invention are capable of modulating activity of HNF-4α receptors in a "co-transfection" assay (also called a "cis-trans" assay), which has been discussed previously. *See e.g.*, Evans *et al.*, *Science*, 240:889-95 (1988); U.S. Patent Nos. 4,981,784 and 5,071,773; Pathirana *et al.*, *Mol. Pharm.* 47:630-35 (1995)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity. Thus, in certain embodiments, such assays are predictive of *in vivo* activity. *See, e.g.*, Berger *et al.*, *J. Steroid Biochem. Molec. Biol.* 41:773 (1992).

[0131] In certain co-transfection assays, two different co-transfection plasmids are prepared. In the first co-transfection plasmid, cloned cDNA encoding an intracellular receptor (*e.g.*, HNF-4α receptor) is operatively linked to a constitutive promoter (*e.g.*,

the SV 40 promoter). In the second co-transfection plasmid, cDNA encoding a reporter protein, such as firefly luciferase (LUC), is operatively linked to a promoter that is activated by a receptor-dependant activation factor. Both co-transfection plasmids are co-transfected into the same cells. Expression of the first co-transfection plasmid results in production of the intracellular receptor protein. Activation of that intracellular receptor protein (*e.g.*, by binding of an agonist) results in production of a receptor-dependant activation factor for the promoter of the second co-transfection plasmid. That receptor-dependant activation factor in turn results in expression of the reporter protein encoded on the second co-transfection plasmid. Thus, reporter protein expression is linked to activation of the receptor. Typically, that reporter activity can be conveniently measured (*e.g.*, as increased luciferase production).

[0132] Certain co-transfection assays can be used to identify agonists, partial agonists, and/or antagonists of intracellular receptors. In certain embodiments, to identify agonists, co-transfected cells are exposed to a test compound. If the test compound is an agonist or partial agonist, reporter activity is expected to be higher compared to co-transfected cells in the absence of the test compound. In certain embodiments, to identify antagonists, the cells are exposed to a known agonist (*e.g.*, the natural ligand for the receptor) in the presence and absence of a test compound. If the test compound is an antagonist, reporter activity is expected to be lower than that of cells exposed only to the known agonist.

[0133] In certain embodiments, compounds of the invention are used to detect the presence, quantity and/or state of receptors in a sample. In certain of such embodiments, samples are obtained from a patient. In certain embodiments, compounds are radio- or isotopically-labeled. For example, compounds of the present invention that

selectively bind HNF-4α receptors may be used to determine the presence or amount of such receptors in a sample, such as cell homogenates and lysates.

[0134] In certain embodiments, the present invention provides for use of both CARLA and mammalian-2-hybrid assays, to characterize the *in vitro* profile of compounds of the invention on a HNF-4α receptor.

Certain Pharmaceutical Agents

[0135] In certain embodiments, at least one selective HNF-4α receptor modulator, or pharmaceutically acceptable salt, ester, amide, and/or prodrug thereof, either alone or combined with one or more pharmaceutically acceptable carriers, forms a pharmaceutical agent. Techniques for formulation and administration of compounds of the present invention may be found for example, in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0136] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0137] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a liquid (*e.g.*, a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[0138] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a solid (*e.g.*, a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0139] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a depot preparation. Certain of such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0140] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical agents including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0141] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises one or more tissue-specific delivery molecules designed to deliver the pharmaceutical agent to specific tissues or cell types.

For example, in certain embodiments, pharmaceutical agents include liposomes coated with a tissue-specific antibody.

[0142] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0143] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release compounds over a period of hours, days, weeks or months.

[0144] Certain compounds used in pharmaceutical agent of the present invention may be provided as pharmaceutically acceptable salts with pharmaceutically compatible

counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.

[0145] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises an active ingredient in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0146] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a prodrug. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (*e.g.*, through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, a prodrug is an ester. In certain embodiments, such prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, the ester in such prodrugs is metabolically hydrolyzed to carboxylic acid. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is metabolized to form the corresponding active form.

[0147] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is useful for treating a conditions or disorder in a mammalian, and particularly in a human patient. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (*e.g.*, intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather than systemic exposures. For example, pharmaceutical agents may be injected directly in the area of desired effect (*e.g.*, in the renal or cardiac area).

[0148] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is administered in the form of a dosage unit (*e.g.*, tablet, capsule, bolus, etc.). In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 1 μg/kg of body weight to about 50 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 2 μg/kg of body weight to about 25 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 10 μg/kg of body weight to about 5 mg/kg of body weight. In certain embodiments, pharmaceutical agents are administered as needed, once per day, twice per day, three times per day, or four or more times per day. It is recognized by those skilled in the art that the particular dose, frequency, and duration of administration depends on a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the pharmaceutical agent.

[0149] In certain embodiments, a pharmaceutical agent comprising a compound of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical agent is formulated by combining one or more compounds of the present invention with one or more pharmaceutically acceptable carriers. Certain of such carriers enable compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. In certain embodiments, pharmaceutical agents for oral use are obtained by mixing one or more compounds of the present invention and one or more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical agents are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (*e.g.*, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[0150] In certain embodiments, dragee cores are provided with coatings. In certain of such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[0151] In certain embodiments, pharmaceutical agents for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or

more compounds of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical agents for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more compounds of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0152] In certain embodiments, pharmaceutical agents are prepared for buccal administration. Certain of such pharmaceutical agents are tablets or lozenges formulated in conventional manner.

[0153] In certain embodiments, a pharmaceutical agent is prepared for administration by injection (*e.g.*, intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical agent comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical agents for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical agents for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical agents for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or

triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0154] In certain embodiments, a pharmaceutical agent is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0155] In certain embodiments, a pharmaceutical agent is prepared for administration by inhalation. Certain of such pharmaceutical agents for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical agents comprise a propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a compound of the invention and a suitable powder base such as lactose or starch.

[0156] In certain embodiments, a pharmaceutical agent is prepared for rectal administration, such as a suppositories or retention enema. Certain of such pharmaceutical agents comprise known ingredients, such as cocoa butter and/or other glycerides.

[0157] In certain embodiments, a pharmaceutical agent is prepared for topical administration. Certain of such pharmaceutical agents comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Pfizer (Morris Plains, New Jersey).

[0158] In certain embodiments, the formulation, route of administration and dosage for a pharmaceutical agent of the present invention can be chosen in view of a particular patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). In certain embodiments, a pharmaceutical agent is administered as a single dose. In certain embodiments, a pharmaceutical agent is administered as a series of two or more doses administered over one or more days.

[0159] In certain embodiments, a pharmaceutical agent of the present invention is administered to a patient between about 0.1% and 500%, more preferably between about 25% and 75% of an established human dosage. Where no human dosage is established, a suitable human dosage may be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies.

[0160] In certain embodiments, a daily dosage regimen for a patient comprises an oral dose of between 0.1 mg and 2000 mg of a compound of the present invention. In certain embodiments, a daily dosage regimen is administered as a single daily dose. In

certain embodiments, a daily dosage regimen is administered as two, three, four, or more than four doses.

[0161] In certain embodiments, a pharmaceutical agent of the present invention is administered by continuous intravenous infusion. In certain of such embodiments, from 0.1 mg to 500 mg of a composition of the present invention is administered per day.

[0162] In certain embodiments, a pharmaceutical agent of the invention is administered for a period of continuous therapy. For example, a pharmaceutical agent of the present invention may be administered over a period of days, weeks, months, or years.

[0163] Dosage amount, interval between doses, and duration of treatment may be adjusted to achieve a desired effect. In certain embodiments, dosage amount and interval between doses are adjusted to maintain a desired concentration on compound in a patient. For example, in certain embodiments, dosage amount and interval between doses are adjusted to provide plasma concentration of a compound of the present invention at an amount sufficient to achieve a desired effect. In certain of such embodiments the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical agents of the present invention are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time.

[0164] In certain embodiments in which a pharmaceutical agent is administered locally, the dosage regimen is adjusted to achieve a desired local concentration of a compound of the present invention.

[0165] In certain embodiments, a pharmaceutical agent may be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0166] In certain embodiments, a pharmaceutical agent is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Certain Combination Therapies

[0167] In certain embodiments, one or more pharmaceutical agents of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more

pharmaceutical agents of the present invention. In certain embodiments, one or more pharmaceutical agents of the present invention is co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the different times. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared separately.

[0168] Examples of pharmaceutical agents that may be co-administered with a pharmaceutical agent of the present invention include, but are not limited to, analgesics (*e.g.*, acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (*e.g.*, ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (*e.g.*, biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (*e.g.*, anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (*e.g.*, biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

Certain Indications

[0169] In certain embodiments, the invention provides methods of treating a patient comprising administering one or more compounds of the present invention. Compounds of the present invention, including, but not limited to, pharmaceutically acceptable salts, solvates and hydrates, are expected to be effective in treating diseases or conditions that are mediated by HNF-4α. Therefore, in certain embodiments, compounds of the invention are effective in treating conditions that are mediated by HNF-4α, including, but not limited to, syndrome X, non-insulin dependent diabetes mellitus, cancer, obesity, cardiovascular disease and dyslipidemia. In certain embodiments, a patient is treated prophylactically to reduce or prevent the occurrence of a condition.

[0170] In certain embodiments, the present invention provides a method of lowering blood glucose levels in a mammal by administering to the patient a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

[0171] In certain embodiments, the present invention provides a method of lowering plasma triglycerides levels in a patient by administering to the mammal a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

[0172] In certain embodiments, the present invention provides a method of increasing insulin levels in a patient by administering to the mammal a pharmaceutically

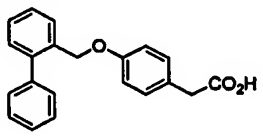
effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

EXAMPLES

[0173] The following examples, including experiments and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

EXAMPLE 1

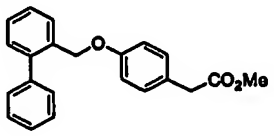
4-(2-phenylbenzyloxy)phenylacetic acid (Compound 1)



[0174] A mixture of 1.2 g (3.6 mmol) of methyl-4-(2-phenylbenzyloxy)phenylacetate, 5 ml of MeOH, 5 ml of THF and 3 ml of a 2N aqueous LiOH solution was stirred for 3 hours at room temperature. The solvents were removed under reduced pressure and the whitish pasty mixture was acidified with 2 N aqueous HCl solution and extracted twice with EtOAc. The organic layers were collected, dried over $MgSO_4$, filtrated and concentrated. The crude acid was recrystallized from Ether/hexane to afford 800 mg (2.5 mmol, yield: 70 %) of 4-(2-phenylbenzyloxy)phenylacetic acid as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.61 (m, 1H), 7.29 (m, 4H), 7.22 (m, 4H), 7.16 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.92 (s, 2H), 3.58 (s, 2H).

EXAMPLE 2

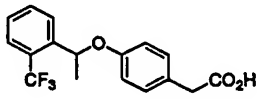
Methyl-4-(2-phenylbenzyloxy)phenylacetate (Compound 2)



[0175] In a round-bottomed flask was added 741 mg (4.5 mmol) of methyl-4-hydroxyphenyl acetate, 6 ml of dry DMF, 0.81 ml (1.1 g, 4.5 mmol) of 2-phenylbenzyl bromide and 2.2 g (6.8 mmol) of Cs_2CO_3. The mixture was stirred at room temperature overnight and water was added (50 ml). The solution was extracted 3 times with EtOAc and the organic layers were collected, washed with water and brine, dried over $MgSO_4$, filtrated and concentrated. The residual oil was then purified over silica gel column chromatography (eluent: 95/5 hexane/EtOAc) to afford 1.36 g (4.1 mmol, yield: 91 %) of methyl-4-(2-phenylbenzyloxy)phenylacetate as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (m, 1H), 7.33 (m, 4H), 7.22 (m, 4H), 7.12 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 4.95 (s, 2H), 3.95 (s, 3H), 3.57 (s, 2H).

EXAMPLE 3

4-[(2-trifluoromethyl)-α-methyl benzyloxy]phenyl acetic acid (Compound 3)

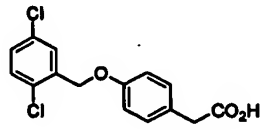


[0176] Compound 3 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and alpha-methyl-2-trifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.08 (d, J =

8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.66 (dd, J = 12.4, 6.2, 1H), 3.51 (s, 2H), 1.63 (t, J = 6.3 Hz, 3H).

EXAMPLE 4

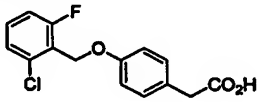
4-(2,5-dichlorobenzyloxy)phenyl acetic acid (Compound 4)



[0177] Compound 4 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,5-dichlorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (s,1H), 7.32 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 5.10 (s, 2H), 3.61 (s, 2H).

EXAMPLE 5

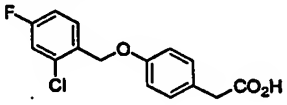
4-(2-chloro-6-fluorobenzyloxy)phenyl acetic acid (Compound 5)



[0178] Compound 5 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-chloro-6-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.05 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 5.16 (s, 2H), 3.61 (s, 2H).

EXAMPLE 6

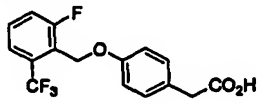
4-(2-chloro-4-fluorobenzyloxy)phenyl acetic acid (Compound 6)



[0179] Compound 6 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-chloro-4-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (dd, J = 8.5, 6.1 Hz, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.16 (dd, J = 8.4, 2.6 Hz, 1H), 7.00 (td, J = 8.3, 2.6 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 5.10 (s, 2H), 3.60 (s, 2H).

EXAMPLE 7

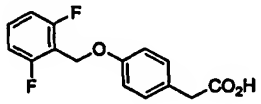
4-(2-fluoro-6-trifluoromethylbenzyloxy) phenyl acetic acid (Compound 7)



[0180] Compound 7 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-fluoro-6-trifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (m, 2H), 7.33 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 5.16 (s, 2H), 3.62 (s, 2H).

EXAMPLE 8

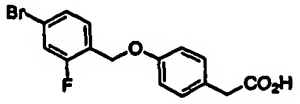
4-(2,6-difluorobenzyloxy)phenyl acetic acid (Compound 8)



[0181] Compound 8 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,6-difluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 6.94 (m, 2H), 5.11 (s, 2H), 3.60 (s, 2H).

EXAMPLE 9

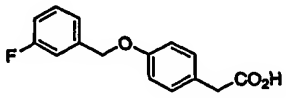
4-(2-fluoro-4-bromobenzyloxy)phenyl acetic acid (Compound 9)



[0182] Compound 9 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 4-bromo-2-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (t, J = 7.9 Hz, 1H), 7.29 (d, J = 10.2 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.06 (s, 2H), 3.59 (s, 2H).

EXAMPLE 10

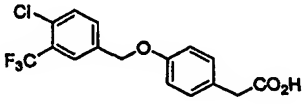
4-(3-fluorobenzyloxy)phenyl acetic acid (Compound 10)



[0183] Compound 10 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 3-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.36 (t, J = 7.38 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 6.3 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 5.03 (s, 2H), 3.60 (s, 2H).

EXAMPLE 11

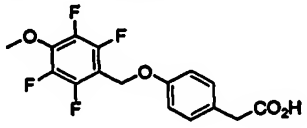
4-(4-chloro-3-trifluoromethylbenzyloxy)phenyl acetic acid (Compound 11)



[0184] Compound 11 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 4-chloro-3-trifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (m, 1H), 7.53 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.06 (s, 2H), 3.61 (s, 2H).

EXAMPLE 12

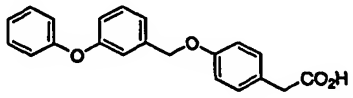
4-(1,2,5,6-tetrafluoro-4-methoxybenzyloxy)phenyl acetic acid (Compound 12)



[0185] Compound 12 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,3,5,6-tetrafluoro-4-methoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 5.09 (s, 2H), 4.10 (s, 3H), 3.62 (s, 2H).

EXAMPLE 13

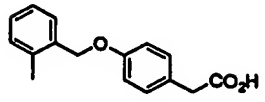
4-(3-phenoxybenzyloxy)phenyl acetic acid (Compound 13)



[0186] Compound 13 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 3-phenoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (m, 3H), 7.20 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 6.4 Hz, 1H), 7.11 (t, J = 6.0 Hz, 1H), 7.09 (m, 1H), 7.02 (d, J = 6.0 Hz, 2H), 6.96 (dd, J = 6.8, 2.0 Hz, 1H), 6.24 (d, J = 5.6 Hz, 2H), 5.02 (s, 2H), 3.60 (s, 2H).

EXAMPLE 14

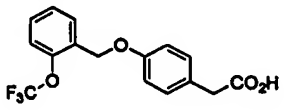
4-(2-methylbenzyloxy)phenyl acetic acid (Compound 14)



[0187] Compound 14 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2methylbenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.0 Hz, 1H), 7.25 (m, 3H), 7.22 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 5.02 (s, 2H), 3.62 (s, 2H), 2.38 (s, 3H).

EXAMPLE 15

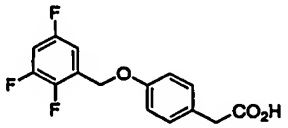
4-(2-trifluoromethoxybenzyloxy)phenylacetic acid (Compound 15)



[0188] Compound 15 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-trifluoromethoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, J = 7.0 Hz, 1H), 7.31 (m, 3H), 7.20 (d, J = 7.3 Hz, 2H), 6.93 (d, J = 7.2 Hz, 2H), 5.14 (s, 2H), 3.59 (s, 2H).

EXAMPLE 16

4-(2,3,5-trifluorobenzyloxy)phenylacetic acid (Compound 16)

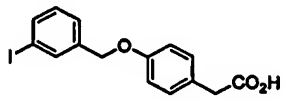


[0189] Compound 16 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,3,5-trifluorobenzyl bromide as

alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (m, 1H), 7.23 (d, J = 7.4 Hz, 2H), 6.97 (m, 1H), 6.93 (d, J = 7.4 Hz, 2H), 5.05 (s, 2H), 3.61 (s, 2H).

EXAMPLE 17

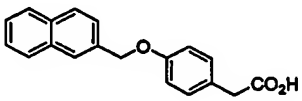
4-(3-iodobenzyloxy)phenylacetic acid (Compound 17)



[0190] Compound 17 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 3-iodobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 4.12 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 4.99 (s, 2H), 3.61 (s, 2H).

EXAMPLE 18

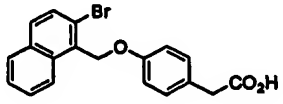
4-(2-naphthalenoxy)phenyl acetic acid (Compound 18)



[0191] Compound 18 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-bromomethylnaphtalene as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89 (d, J = 3.0 Hz, 1H), 7.86 (m, 3H), 7.53 (dd, J 10.0, 1.5 Hz, 1H), 7.50 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 5.22 (s, 2H), 3.61 (s, 2H).

EXAMPLE 19

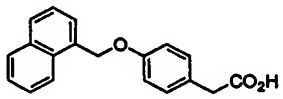
4-[1-(2-bromo)naphthalenoxy]phenylacetic acid (Compound 19)



[0192] Compound 19 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 1-bromo-2-bromomethylnaphtalene as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 4.5 Hz, 1H), 7.82 (d, J = 4.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.76 (t, J = 7.0 Hz, 1H), 7.54 (t, J = 7.0 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 5.38 (s, 2H), 3.61 (s, 2H).

EXAMPLE 20

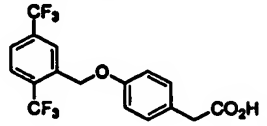
4-(1-naphthalenoxy)phenylacetic acid (Compound 20)



[0193] Compound 20 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 1-bromomethylnaphtalene as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, J = 1.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H), 7.48 (dd, J = 8.5, 2.0 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 5.24 (s, 2H), 3.63 (s, 2H).

EXAMPLE 21

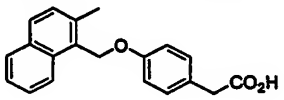
4-(2,5-bistrifluoromethylbenzyloxy)phenyl acetic acid (Compound 21)



[0194] Compound 21 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,5-bistrifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 5.28 (s, 2H), 3.62 (s, 2H).

EXAMPLE 22

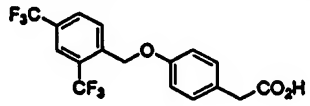
4-[1-(2-methyl)naphthalenoxy]phenylacetic acid (Compound 22)



[0195] Compound 22 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2-methyl-1-chloromethylnaphtalene as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 5.46 (s, 2H), 3.66 (s, 2H), 2.59 (s, 3H).

EXAMPLE 23

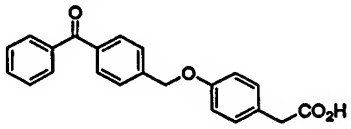
4-(2,4-bistrifluoromethylbenzyloxy)phenylacetic acid (Compound 23)



[0196] Compound 23 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 2,4-bistrifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.32 (s, 2H), 3.61 (s, 2H).

EXAMPLE 24

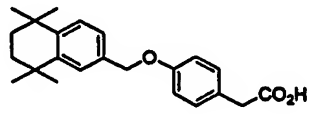
4-(4-benzoylbenzyloxy)phenylacetic acid (Compound 24)



[0197] Compound 24 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 4-bromomethyl benzophenone as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, J = 8.2 Hz, 2H), 7.81 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 5.15 (s, 2H), 3.61 (s, 2H).

EXAMPLE 25

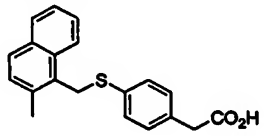
4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthyloxy)]phenylacetic acid (Compound 25)



[0198] Compound 25 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 3-bromomethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphtalene as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.23 (m, 2H), 6.97 (d, J = 8.5 Hz, 2H), 4.97 (s, 2H), 3.61 (s, 2H), 1.69 (m, 4H), 1.29 (s, 6H), 1.28 (s, 6H).

EXAMPLE 26

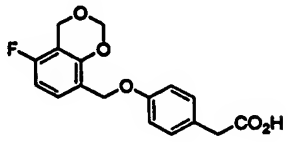
4-[1-(2-methyl)naphthalenemethanethiol]phenyl acetic acid (Compound 26)



[0199] Compound 26 was synthesized according to the procedure described in Example 1 using 4-thiophenyl acetic acid and 1-methyl-2-chloromethylnaphtalene as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 9.1 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 9.1Hz, 1H), 7.42 (dd, J = 7.1, 1.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 4.58 (s, 2H), 3.66 (s, 2H), 2.50 (s, 3H).

EXAMPLE 27

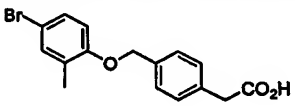
4-(4-fluoro-2,3-bezo-1,3-dioxanyloxy)phenylacetic acid (Compound 27)



[0200] Compound 27 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and (5-fluoro-4H-1,3-benzodioxin-8-yl)chloromethyl as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.51 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 5.23 (s, 2H), 5.01 (s, 2H), 4.87 (s, 2H)3.57 (s, 2H).

EXAMPLE 28

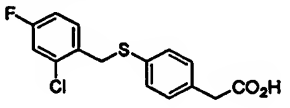
4-(2-methyl-4-bromobenzyloxy)phenylacetic acid (Compound 28)



[0201] Compound 28 was synthesized according to the procedure described in Example 1 using 4-hydroxyphenyl acetic acid and 4-bromo-2-methylbenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 8.1, 1.5 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 5.25 (s, 2H), 3.57 (s, 2H), 2.01 (s, 3H).

EXAMPLE 29

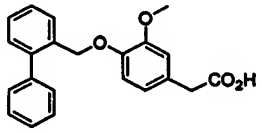
4-(2-chloro-4-fluorobenzylmercapto)phenylacetic acid (Compound 29)



[0202] Compound 29 was synthesized according to the procedure described in Example 1 using 4-thiophenyl acetic acid and 2-chloro-4-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.19 (m, 1H), 7.11 (dd, J = 8.5, 2.5 Hz, 1H), 6.87 (dt, J = 8.3, 2.5 Hz, 1H), 4.15 (s, 2H), 3.62 (s, 2H).

EXAMPLE 30

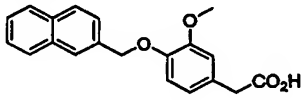
3-methoxy-4-(2-phenylbenzyloxy)phenylacetic acid (Compound 30)



[0203] Compound 30 was synthesized according to the procedure described in Example 1 using ethyl homovanillate and 2-phenylbenzyl bromide as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (m, 1H), 7.48 (m, 8H), 6.79 (d, J = 1.9 Hz, 1H), 6.70 (dd, J = 8.1, 2.0 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.00 (s, 2H), 3.85 (s, 3H), 3.55 (s, 2H).

EXAMPLE 31

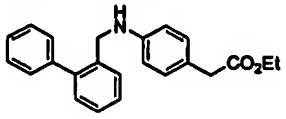
3-methoxy-4-(2-naphthalenoxy)phenylacetic acid (Compound 31)



[0204] Compound 31 was synthesized according to the procedure described in Example 1 using ethyl homovanillate and 2-bromomethylnaphthalene as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.47 (m, 2H), 6.87 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 1.8 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 5.31 (s, 2H), 3.90 (s, 3H), 3.57 (s, 2H).

EXAMPLE 32

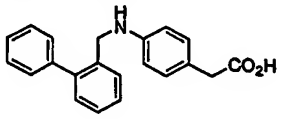
Ethyl-4-(2-phenyl)benzylamino phenyl acetic acid (Compound 32)



[0205] A mixture of 296 mg (1.65 mmol) of ethyl-4-aminophenylacetic acid, 342 mg (1.65 mmol, 0.25 ml) of 2-phenylbenzyl bromide and 1.08 g (3.3 mmol) of Cs_2CO_3 in 3 ml of dry DMF was heated to 50° C overnight. After cooling at room temperature, water was added and the solution was extracted with EtOAc (3 times 5 ml). The organic layers were collected, washed with water (2 times) and brine, then dried over $MgSO_4$. After filtration and concentration, the crude oil as purified over silica gel column chromatography (eluent: 90/10 and 80/20 hexane/EtOAc) to afford 456 mg (1.32 mmol, yield: 80 %) of ethyl-4-(2-phenyl)benzylamino phenyl acetic acetate as a clear oil.. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.51 (m, 1H), 7.37 (m, 7H), 7.30 (m, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 4.42 (dd, J = 14.2, .1 Hz, 2H), 4.22 (s, 2H), 3.50 (s, 2H), 1.25 (t, J = 7.1 Hz, 3H).

EXAMPLE 33

4-(2-phenyl)benzylamino phenyl acetic acid (Compound 33)

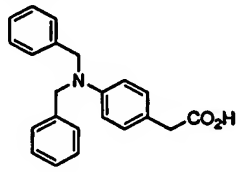


[0206] A mixture of 300 mg (0.868 mmol) in 5 ml of MeOH, 3 ml of THF and 3 ml of aqueous LiOH (2N) was stirred at room temperature for 12 hours. The solvents were evaporated and the mixture was neutralized to pH 7 with 2N aqueous HCl. The resulting solution was extracted with EtOAc (3 times) and the organic layers were dried

over $MgSO_4$. After filtration and concentration, the crude acid was recrystallized from ether to afford 2.7 mg (0.65 mmol, yield: 75 %) of 4-(2-phenyl)benzylamino phenyl acetic acid as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.51 (m, 1H), 7.37 (m, 7H), 7.30 (m, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 4.22 (s, 2H), 3.50 (s, 2H).

EXAMPLE 34

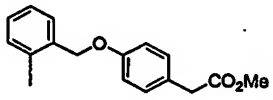
4-(*N*,*N*-dibenzylamino)phenylacetic acid (Compound 34)



[0207] Compound 34 was synthesized according to the procedure described in Example 33 using 4-aminophenyl acetic acid and an excess of benzyl bromide as alkylating reagent. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J = 7.8 Hz, 2H), 7.27 (m, 12H), 4.89 (s, 4H), 3.30 (s, 2H).

EXAMPLE 35

Methyl-4-(2-iodobenzyloxy)phenyl acetate (Compound 35)

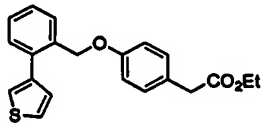


[0208] In a round-bottomed flask was added 3.50 g (21.0 mmol) of methyl-4-hydroxyphenyl acetate, 30 ml of dry DMF, 6.25 g (21.0 mmol) of 2-iodobenzyl bromide and 9.5 g (29.2 mmol) of Cs_2CO_3. The mixture was stirred at room temperature overnight and water was added (100 ml). The solution was extracted 3 times with EtOAc and the organic layers were collected, washed with water and brine, dried over

$MgSO_4$, filtrated and concentrated. The residual oil was then purified over silica gel column chromatography (eluent: 95/5 hexane/EtOAc) to afford 7.71 g (21.1 mmol, yield: 96 %) of methyl-4-(2-iodobenzyloxy)phenylacetate as an oil that solidify upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.5 (s, 1H), 7.66 (dd, J = 8.0, 1.0 Hz, 1H), 7.39 (dd, J = 8.0, 1.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 7.10 (t, J = 8.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 4.99 (s, 2H), 3.69 (s, 3H), 3.58 (s, 2H).

EXAMPLE 36

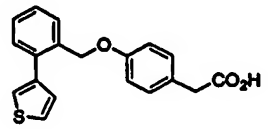
Ethyl-4-(2-(3-thienyl)benzyloxy)phenyl acetate (Compound 36)



[0209] A mixture of 171 mg (0.45 mmol) of methyl-4-(2-iodobenzyloxy)phenylacetate, 86 mg (0.67 mmol) of 3-thiophene boronic acid, 26 mg (0.2 mmol)of $Pd(PPh_3)_4$ in 5 ml of toluene, 4 ml of EtOH and 0.5 ml of 2N aqueous Na_2CO_3 was heated to reflux overnight. After cooling and evaporation of the solvents, the mixture was purified by SiO_2 column chromatography (eluent: 91/10 hexane/EtOAc) to afford 127 mg (0.36 mmol, yield: 80 %) of ethyl-4-(2-(3-thienyl)benzyloxy)phenyl acetate as a pasty oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (m, 1H), 7.43 (m, 1H), 7.35 (m, 2H), 7.30 (m, 1H), 7.24 (m, 1H), 7.21 (m, 1H), 7.20 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.95 (s, 2H), 4.32 (dd, J = 14.0. 7.0 Hz, 2H), 3.59 (s, 2H), 1.13 (t, J = 7.1 Hz, 3H).

EXAMPLE 37

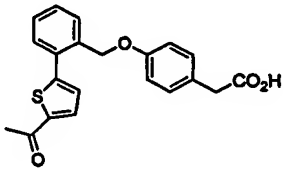
4-(2-(3-thienyl)benzyloxy)phenyl acetic acid (Compound 37)



[0210] Compound 37 was synthesized according to the saponification procedure described in Example 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (m, 1H), 7.42 (m, 1H), 7.33 (m, 2H), 7.30 (m, 1H), 7.28 (m, 1H), 7.24 (m, 1H), 7.23 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.95 (s, 2H), 3.59 (s, 2H).

EXAMPLE 38

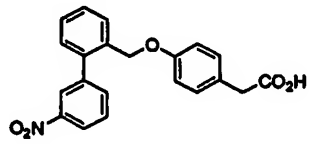
4-[2-(5-acetyl-2-thienyl)]benzyloxy phenylacetic acid (Compound 38)



[0211] Compound 38 was synthesized according to the procedure described in Example 37 using 5-acetylthiophene boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, J = 3.9 Hz, 1H), 7.59 (m, 1H), 7.50 (m, 1H), 7.45 (m, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 4.0 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.02 (s, 2H), 3.60 (s, 2H), 2.55 (s, 3H).

EXAMPLE 39

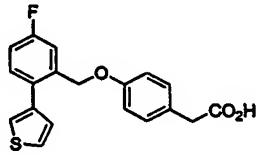
4-[2-(3-nitro)phenylbenzyloxy]phenyl acetic acid (Compound 39)



[0212] Compound 39 was synthesized according to the procedure described in Example 37 using 3-nitrophenyl boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (s, 1H), 8.20 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.61 (m, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.47 (m, 2H), 7.35 (m, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.86 (s, 2H), 3.58 (s, 2H).

EXAMPLE 40

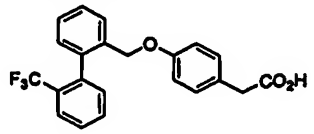
4-[2-(3-thienyl)-5-fluorobenzyl]phenyl acetic acid (Compound 40)



[0213] Compound 40 was synthesized according to the procedure described in Example 37 using 3-thiophene boronic acid as coupling reagent and methyl(2-bromo-5-fluorobenzyloxy)benzoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J = 5.2 Hz, 1H), 7.37 (t, J = 5.9 Hz, 1H), 7.32 (dd, J = 9.6, 2.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 7.15 (dd, J = 4.9, 1.2 Hz, 1H), 7.82 (td, J = 8.3, 21.6 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 4.94 (s, 2H), 3.59 (s, 2H).

EXAMPLE 41

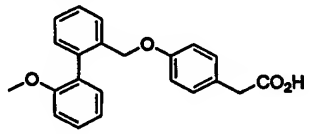
4-[2-(2-trifluoromethyl)phenylbenzyloxy]phenyl acetic acid (Compound 41)



[0214] Compound 41 was synthesized according to the procedure described in Example 37 using 2-trifluoromethylphenyl boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.53 (m, 1H), 7.46 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 4.72 (d, J = 8.0 Hz, 1H), 4.66 (d, J = 8.0 Hz, 1H), 3.52 (s, 2H).

EXAMPLE 42

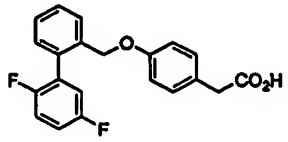
4-[2-(2-methoxy)phenylbenzyloxy]phenyl acetic acid (Compound 42)



[0215] Compound 42 was synthesized according to the procedure described in Example 37 using 2-methoxybenzene boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J = 7.3 Hz, 1H), 7.37 (m, 3H), 7.25 (m, 1H), 7.21 (dd, J = 7.4, 1.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 4.98 (d, J = 11.9 Hz, 1H), 4.80 (d, J = 11.9 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 2H).

EXAMPLE 43

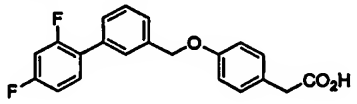
4-[2-(2,5-difluorophenyl)benzyloxy]phenylacetic acid (Compound 43)



[0216] Compound 43 was synthesized according to the procedure described in Example 37 using 2,5-difluorobenzene boronic acid as coupling reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, J = 6.8 Hz, 1H), 7.45 (td, J = 6.0, 1.2 Hz, 1H), 7.41 (td, J = 6.4, 1.2 Hz, 1H), 7.28 (dd, J = 5.2, 1.2 Hz, 1H), 7.14 (d, J = 6.8 Hz, 2H), 7.07 (m, 1H), 7.03 (m, 2H), 6.79 (d, J = 6.8 Hz, 2H), 4.91 (s, 2H), 3.57 (s, 2H).

EXAMPLE 44

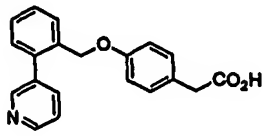
4-[3-(2,4-difluorophenyl)benzyloxy]phenylacetic acid (Compound 44)



[0217] Compound 44 was synthesized according to the procedure described in Example 37 using 2,5-difluorobenzene boronic acid and methyl 4-(3-iodobenzyloxy)phenyl acetate as coupling reagents. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56 (m, 1H), 7.45 (m, 5H), 7.22 (d, J = 7.4 Hz, 2H), 6.97 (d, J = 7.4 Hz, 2H), 6.91 (m, 1H), 5.19 (s, 2H), 3.61 (s, 2H).

EXAMPLE 45

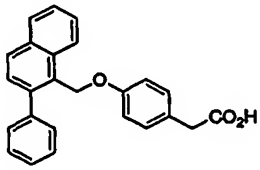
4-(3-pyridylbenzyloxy)phenylacetic acid (Compound 45)



[0218] Compound 45 was synthesized according to the procedure described in Example 37 using 3-pyridyl boronic acid as coupling reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 6H), 7.29 (m, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.09 (m, 1H), 6.79 (d, J = 8.6 Hz, 2H), 4.90 (s, 2H), 3.57 (s, 2H).

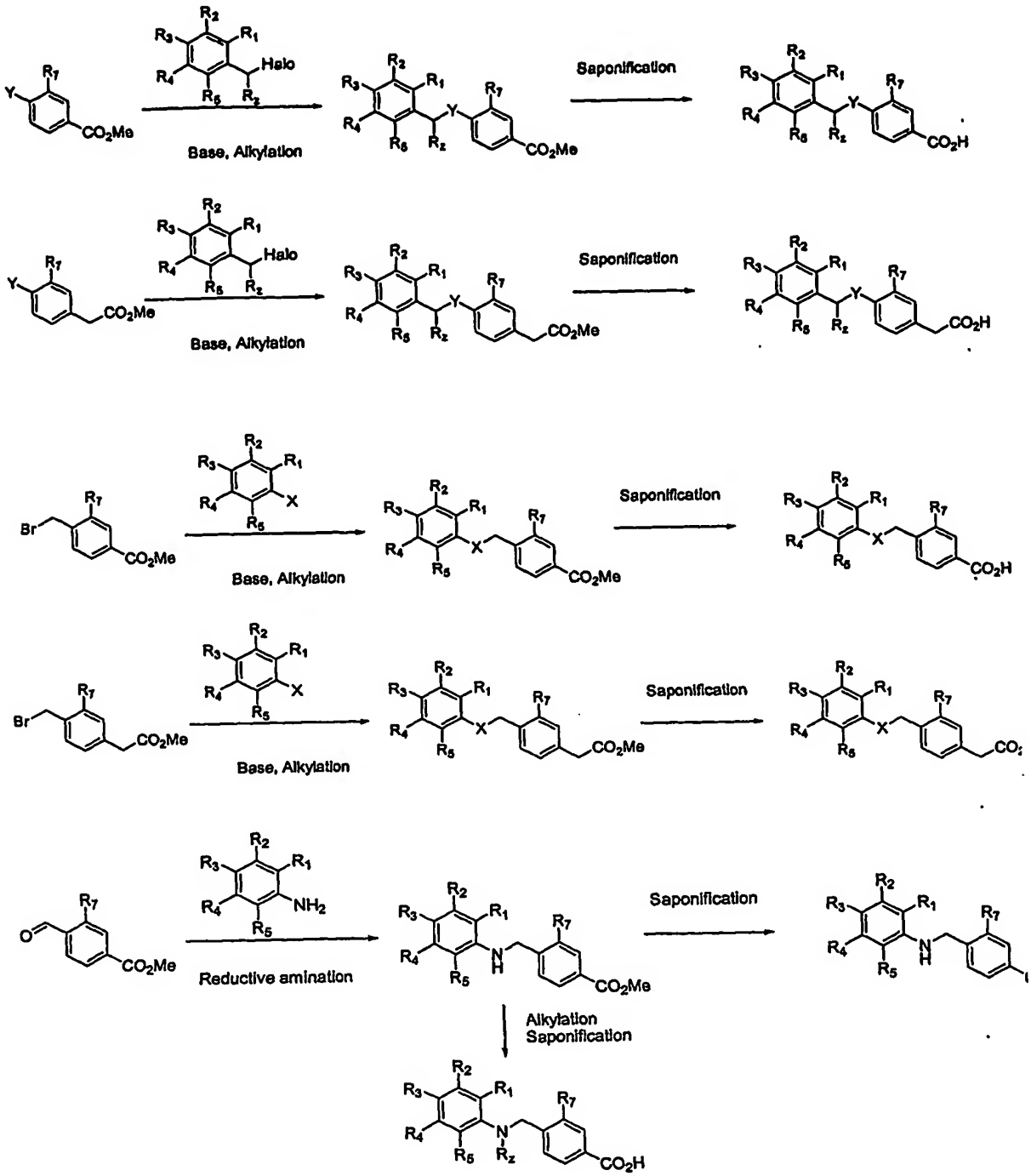
EXAMPLE 46

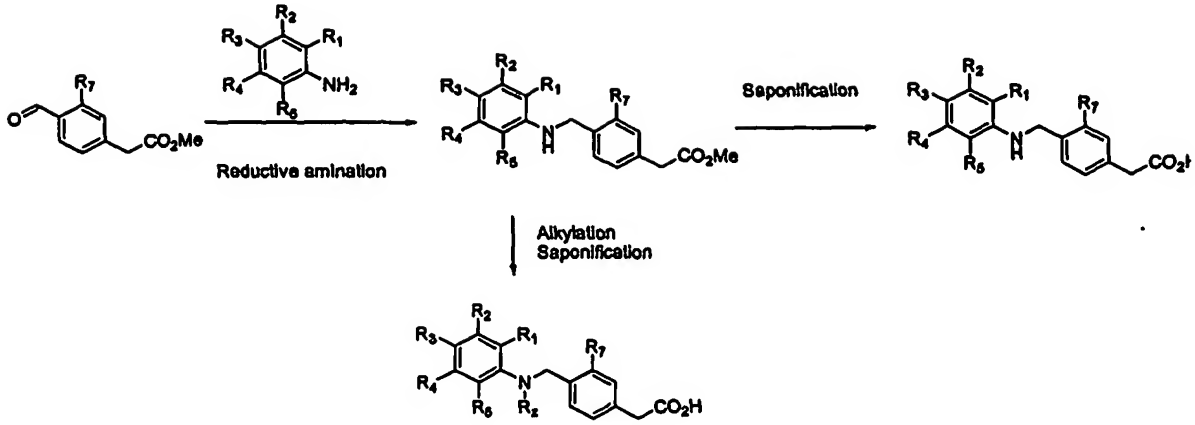
4-[1-(2-phenyl)naphthalenoxy]phenylacetic acid (Compound 46)



[0219] Compound 46 was synthesized according to the procedure described in Example 37 using benzene boronic acid and methyl-4-(2-bromonaphthyloxymethyl)phenyl acetic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.47 (m, 5H), 7.38 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 6.3 Hz, 2H), 7.13 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 4.91 (s, 2H), 3.90 (s, 3H), 3.56 (s, 2H).

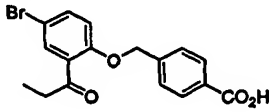
Benzoic acids may be synthesized using the following schemes.


Base, Alkylation
Saponification
Base, Alkylation
Saponification
Base, Alkylation
Saponification
Base, Alkylation
Saponification
Reductive amination
Saponification
Alkylation
Saponification



EXAMPLE 47

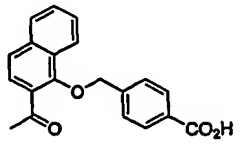
4-{[4-bromo-(2-propan-1-one)]phenyloxy}methyl benzoic acid (Compound 47)



[0220] 47 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 4-bromo-2-propionyl phenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 2.5 Hz, 1H), 7.52 (dd, J = 8.8 Hz, 2H), 7.48 (m, 1H), 6.85 (d, J = 8.8 Hz, 1H), 5.21 (s, 2H), 2.96 (dd, J = 14.4, 7.2 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H).

EXAMPLE 48

4-(2-acetyl-1-naphthyloxy)methyl benzoic acid (Compound 48)

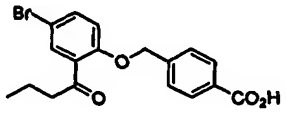


[0221] Compound 48 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 2-acetyl-1-naphthol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 9.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 2H),

7.67 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.47 (t, J = 8.4 Hz, 2H), 7.38 (t, J = 7.8 Hz, 1H), 5.38 (s, 2H), 2.62 (s, 3H).

EXAMPLE 49

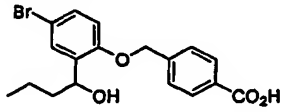
4-{[4-bromo-(2-butan-1-one)]phenyloxy}methyl benzoic acid (Compound 49)



[0222] Compound 49 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 4-bromo-2-butyryl phenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 2.5 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.49 (dd, J = 8.7, 2.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.22 (s, 2H), 2.92 (t, J = 7.3 Hz, 2H), 1.65 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

EXAMPLE 50

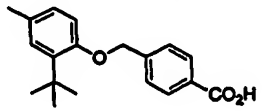
4-{[4-bromo-(2-butan-1-ol)]phenyloxy}methylbenzoic acid (Compound 50)



[0223] Compound 50 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 4-bromo-2-(2-hydroxybutyl)-4-bromophenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.32 (dd, J = 8.8, 2.4 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.16 (s, 2H), 5.02 (t, J = 5.0 Hz, 1H), 1.75 (dd, J = 15.8, 7.9 Hz, 2H), 1.55 (m, 3H), 0.93 (t, J = 7.4 Hz, 3H).

EXAMPLE 51

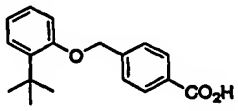
4-(2-*tert*-butyl-4-methylphenyl)phenyloxymethyl benzoic acid (Compound 51)



[0224] Compound 51 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 2-tert-butyl-4-methylphenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 6.73 (broad s, 1H), 5.19 (s, 2H), 2.31 (s, 3H), 1.40 (s, 9H).

EXAMPLE 52

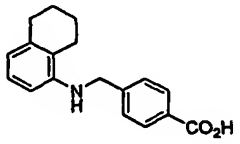
4-(2-tert-butylphenoxymethyl)benzoic acid (Compound 52)



[0225] Compound 52 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 2-tert-butylphenol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.8, 1.7 Hz, 1H), 7.17 (td, J = 8.0, 1.7 Hz, 1H), 6.94 (td, J = 8.0, 1.7 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 5.21 (s, 2H), 1.42 (s, 9H).

EXAMPLE 53

4-(5,6,7,8-tetrahydro1-naphthylaminomethyl)benzoic acid (Compound 53)

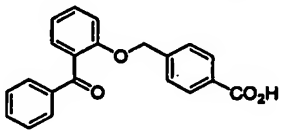


[0226] Compound 53 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 5,6,7,8-tetrahydro1-naphthyamine. ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 6.97 (dd, J = 7.9, 7.7 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 6.35 (d, J = 7.7 Hz, 1H), 4.46 (s, 2H), 2.76 (dd, J = 5.9, 5.9 Hz, 2H), 2.47 (dd, J = 6.3, 6.3 Hz, 2H), 1.91 (m, 2H), 1.77 (m, 2H).

EXAMPLE 54

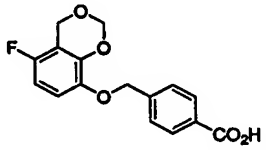
4-(2-benzophenoylphenoxymethyl)benzoic acid (Compound 54)



[0227] Compound 51 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 1-hydroxy benzophenone. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.48 (m, 4H), 7.11 (t, J = 7.4 Hz, 1H), 7.03 (m, 3H), 5.08 (s, 2H).

EXAMPLE 55

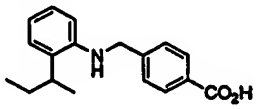
4-[(5-fluoro-4H-1,3-benzodioxin-8-yl)methoxy]benzoic acid (Compound 55)



[0228] Compound 55 was synthesized according to the procedure described in Example 3 using 4-hydroxy benzoate and (5-fluoro-4H-1,3-benzodioxin-8-yl)chloromethyl. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.9 Hz, 2H), 7.12 (m, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.68 (m, 1H), 5.28 (s, 2H), 5.14 (s, 2H), 4.91 (s, 2H).

EXAMPLE 56

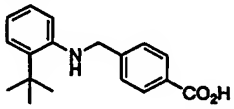
4-[2-(1-methylpropyl)phenylamino]methyl benzoic acid (Compound 56)



[0229] Compound 56 was synthesized according to the procedure described in Example 3 using 4-hydroxy benzoate and 2-(2-methylpropyl)aniline. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.13 (dd, J = 7.9, 1.4 Hz, 1H), 7.05 (m, 1H), 6.76 (dd, J = 7.4, 7.4 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 4.47 (s, 2H), 2.67 (m, 1H), 1.73 (m, 1H), 1.62 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H).

EXAMPLE 57

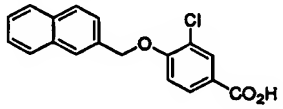
4-(2-tert-butylphenylamino)methyl benzoic acid (Compound 57)



[0230] Compound 57 was synthesized according to the procedure described in Example 3 using 4-hydroxy benzoate and 2-tert-butylaniline. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 7.9, 1.4 Hz, 1H), 7.07 (m, 1H), 6.73 (dd, J = 7.3, 7.3 Hz, 1H), 6.56 (d, J = 7.9 Hz, 1H), 4.51 (s, 2H), 1.46 (s, 9H).

EXAMPLE 58

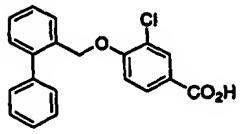
4-[(2-methyl-1-naphthyloxy)methyl]benzoic acid (Compound 58)



[0231] Compound 58 was synthesized according to the procedure described in Example 3 using 3-chloro-4-hydroxy benzoate and 2-chloromethylmaphthalene. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.6, 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.22 (dd, J = 8.7, 2.0 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 5.18 (s, 2H), 1.69 (broad s, 4H), 1.28 (s, 12H).

EXAMPLE 59

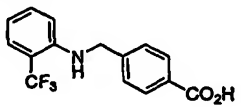
4-[(2-methyl-1-naphthyloxy)methyl]benzoic acid (Compound 59)



[0232] Compound 59 was synthesized according to the procedure described in Example 3 using 3-chloro-4-hydroxy benzoate and 2-phenyl benzyl bromide. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 8.6, 2.0 Hz, 1H), 7.67 (m, 1H), 7.36 (m, 9H), 6.76 (d, J = 8.6 Hz, 1H), 5.09(s, 2H).

EXAMPLE 60

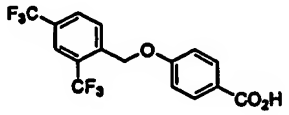
4-(2-trifluoromethylanilinomethyl)benzoic acid (Compound 60)



[0233] Compound 60 was synthesized according to the procedure described in Example 3 using 4-bromomethyl benzoate and 2-trifluoromethyl aniline. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.28 (dd, J = 8.3 Hz, 1H), 6.75 (dd, J = 7.6 Hz), 6.58 (d, J = 8.3 Hz, 1H), 4.53 (s, 2H).

EXAMPLE 61

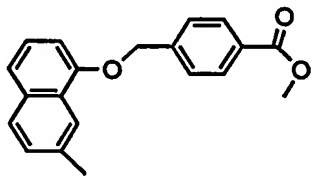
4-(2,4bistrifluoromethylbenzyloxy)benzoic acid (Compound 61)



[0234] Compound 61 was synthesized according to the procedure described in Example 3 using 4-hydroxy benzoate and 2,4-bistrifluoromethylbenzyl bromide. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.8 Hz, 2H), 7.97 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 5.39 (s, 2H).

EXAMPLE 62

Methyl-4-(2-methyl-1-naphthyloxymethyl)benzoate (Compound 62)

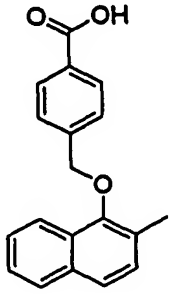


[0235] To a mixture of 2methylnaphthol (300mgs, 1.9mmol), and methy-4-bromomethylbenzoicacid (478mgs, 2.1mmol) in 6mls of dry DMF under nitrogen was added potassium carbonate (524 mgs, 4mmol). The reaction was allowed to stir at 70C for 12 hrs at which time the reaction was quenched with water, extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced pressure to an oil. The oil was purified using flash silica column chromatography (gradient Hexanes to 10% EtoAc/Hexanes) affording the desired product (490mgs, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) 8.12 (d, J = 8.2, 2H), 8.06 (d, J = 8.2, 1H), 7.83 (d, J = 7.6, 1H), 7.64 (d, J = 8.5,

2H), 7.58 (d, J = 8.2, 1H), 7.46 (m, 2H), 7.32 (d, J = 8.2, 1H), 5.07 (s, 2H), 3.95 (s, 3H), 2.45 (s, 3H).

EXAMPLE 63

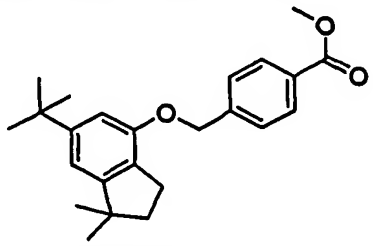
4-(2-methyl-1-naphthyloxymethyl)benzoic acid (Compound 63)



[0236] To a solution of the methylnaphthylbenzoicacidmethylester (490mgs, 1.7mmol) in a 2:1:1 mixture of THF/Water/Ethanol was added Lithium hydroxide (354 mgs, 8.4 mmol). The reaction was allowed to stir at reflux for 3 hrs at which time the reaction was quenched with water and acidified to pH 1 using 6N HCl. The solution was extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced pressure to the desired product which was recrystallized from ethylacetate/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) 8.21 (d, J = 8.2, 2H), 8.07 (d, J = 8.2, 1H), 7.84 (d, J = 7.3, 1H), 7.69 (d, J = 7.9, 2H), 7.59 (d, J = 8.5, 1H), 7.46 (m, 2H), 7.34 (d, J = 8.5, 1H), 5.10 (s, 2H), 2.46 (s, 3H).

EXAMPLE 64

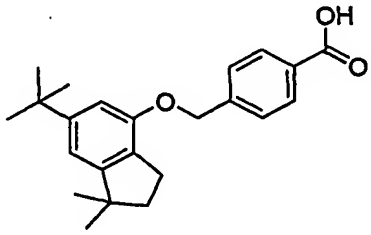
Methyl-4-(3-tert-butyl-5,5-dimethylindanoxymethyl)benzoate (Compound 64)



[0237] To a mixture of the phenol (200mgs, 0.9 mmol), and methy-4-bromomethylbenzoicacid (231mgs, 1.0mmol) in 4mls of dry DMF under nitrogen was added potassium carbonate (253 mgs, 1.8mmol). The reaction was allowed to stir at 70C for 12 hrs at which time the reaction was quenched with water, extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced pressure to an oil. The oil was purified using flash silica column chromatography (gradient Hexanes to 10% EtoAc/Hexanes) affording the desired product (152mgs, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) 8.05 (d, J = 10.0, 2H), 7.53 (d, J = 10.0, 2H), 6.81 (d, J = 2.5, 1H), 6.74 (d, J = 2, 1H), 5.15 (s, 2H), 3.93 (s, 3H), 2.87 (t, J = 7.5, 2H), 1.90 (t, J = 8, 2H), 1.29 (s, 9H), 1.26 (s, 6H).

EXAMPLE 65

4-(3-tert-butyl-5,5-dimethylindanoxymethyl)benzoic acid (Compound 65)

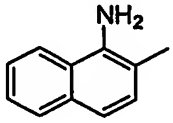


[0238] To a solution of the benzoicacidmethylester (118mgs, 0.3 mmol) in a 1:1:1 mixture of THF/Water/Ethanol was added Lithium hydroxide (68 mgs, 1.6 mmol).

The reaction was allowed to stir at reflux for 3 hrs at which time the reaction was quenched with water and acidified to pH 1 using 6N HCl. The solution was extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced pressure to the desired product which was recrystalized from ethylacetate/hexanes. ^{1}H NMR (500 MHz, DMSO) 7.96 (d, J = 8.24, 2H), 7.58 (d, J = 8.2, 2H), 6.8 (s, 1H), 6.78 (s, 1H), 5.21 (s, 2H), 2.76 (t, J = 7.0, 2H), 1.86 (t, J = 7.0, 2H), 1.24 (s, 9H), 1.20 (s, 6H).

EXAMPLE 66

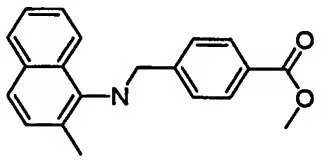
1-amino-2-methyl naphthalene (Compound 66)



[0239] To a solution of 1-nitro,2-methylnaphthyl (2g, 11mmol) in 20 mls ethylacetate was added approximately Palladium/carbon. The reaction vessel atmosphere was evacuated and the mix was put under hydrogen atmosphere using a balloon. The reaction was allowed to stir 72 hrs at which time the mix was filtered through celite packed plug (hexanes/ethylacetate) affording the desired product as a brown oil (1.67g, 99%). 1H NMR (500 MHz, CDCl3) 7.77 (m, 2H), 7.41 (m, 2H), 7.24 (m, 2H), 4.10 (m, 2H), 2.35 (s, 3H).

EXAMPLE 67

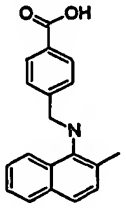
Methyl-4-(2-methyl-1-aminonaphthylaminomethyl)benzoate (Compound 67)



[0240] The aniline (1.6g, 10mmol) was taken up in dichloroethane(50mls) under nitrogen and 4methylformylbenzoate (1.84g, 11mmol) was added, followed by addition of a catalytic amount of acetic acid(0.6mls) and sodium triacetoxyborohydride (4.32g, 20mmol). The reaction was allowed to stir 36 hrs at which time the reaction was quenched with water, and the pH brought to 7 using 6N sodium hydroxide. The water/ethylacetate mix was extracted three times with ethyl acetate (100mls/X3) from water, the organic layers were collected and washed with brine, dried over solid sodium sulfate, filtered, and concentrated under reduced pressure to a yellow oil. The oil was first purified using flash silica column chromatography (EtoAc/Hex) affording product (1.45g, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (d, J= 8.2, 1H), 8.02 (d, J= 8.0, 2H), 7.81 (d, J= 7.9, 1H), 7.50 (d, J= 8.2, 1H), 7.44 (m, 2H), 7.46 (d, J= 8.2, 2H), 7.27 (d, J = 8.2, 1H), 4.36 (s, 2H), 3.60 (bs, 1H), 3.93 (s, 3H), 2.32 (s, 3H).

EXAMPLE 68

4-(2-methyl-1-aminonaphthylaminomethyl)benzoic acid (Compound 68)

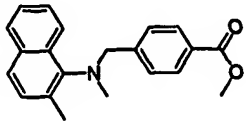


[0241] To a solution of the aminomethylnaphthylester (204mgs, 0.067mmol) in a 1:1:1 mixture of THF/Water/Ethanol was added Lithium hydroxide (140 mgs, 3.3 mmol). The reaction was allowed to stir at reflux for 3 hrs at which time the reaction was quenched with water and acidified to pH 7 using 6N HCl. The solution was extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced

pressure to the desired product. The product was recrystalized from hexanes/ethylacetate. ^{1}H NMR (500 MHz, $CDCl_3$) 8.12 (d, J = 6.8, 1H), 8.10 (d, J = 7.81, 2H), 7.82 (d, J = 7.8, 1H), 7.51 (d, J = 8.3, 2H), 7.45 (m, 3H), 7.28 (d, J = 8.3, 1H) 4.39 (s, 2H), 2.33 (s, 3H).

EXAMPLE 69

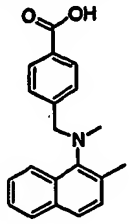
Methyl-4-(2-methyl-1-N-ethylaminonaphthylaminomethyl)benzoate (Compound 69)



[0242] To a solution of methanol and methylene chloride (1:1;10mls) was added the benzylaminomethylester (250mgs, 0.8mmol), and formaldehyde (0.07mls, 2.5mmol), followed by addition of sodium cyanoborohydride (257mgs, 4.1mmol). The reaction was allowed to stir 12 hrs at which time the reaction was quenched with water, and the pH brought to 7 using 6N sodium hydroxide. The water/ethylacetate mix was extracted three times with ethyl acetate (100mls/X3) from water, the organic layers were collected and washed with brine, dried over solid sodium sulfate, filtered, and concentrated under reduced pressure to a white solid (156mgs, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) 8.26 (s, J = 8.24, 1H), 8.02 (d, J = 8.2, 2H), 7.82 (d, J = 8.2, 1H), 7.60 (d, J = 8.2, 1H), 7.49 (d, J = 8.2, 2H), 7.46 (m, 2H), 7.28 (d, J = 8.5, 1H), 4.41 (s, 2H), 3.92 (s, 3H), 2.89 (s, 3H), 2.48 (s, 3H).

EXAMPLE 70

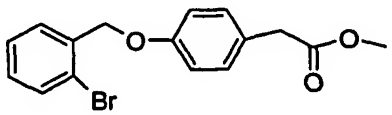
4-(2-methyl-1-N-ethylaminonaphthylaminomethyl)benzoic acid (Compound 70)



[0243] To a solution of the methylaminomethylnaphthylester (156mgs, 0.49 mmol) in a 1:1:1 mixture of THF/Water/Ethanol was added lithium hydroxide (103 mgs, 2.4 mmol). The reaction was allowed to stir at reflux for 5 hrs at which time the reaction was quenched with water and acidified to pH 7 using 6N HCl. The solution was extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over solid sodium sulphate, filtered, and concentrated under reduced pressure to the desired product. ^{1}H NMR (500 MHz, DMSO) 12.83 (bs, 1H), 8.24 (d, J = 8.6, 1H), 7.92 (d, J = 8.2, 2H), 7.87 (d, J = 8.2, 2H), 7.66 (d, J = 8.2, 1H), 7.52 (d, J = 8.2, 2H), 7.49 (m, 2H), 7.33 (d, J = 8.2, 1H), 4.40 (d, J = 4.0, 2H), 2.84 (s, 3H), 2.46 (s, 3H).

EXAMPLE 71

4-(2-Bromo-benzyloxy)-phenyl]-acetic acid methyl ester

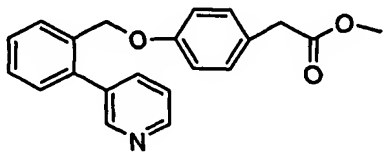


[0244] 1-Bromo-2-bromomethyl-benzene (14.7 g, 50mmol), (4-Hydroxy-phenyl)acetic acid-methyl ester (8.31g, 50mmol) and potassium carbonate (7.60g, 55mmol) are suspended in DMF (100mL) and are allowed to stir for 16 hrs. The reaction

is extracted between ether and water and the organic layers are washed with brine and dried over sodium sulfate. The organic layer is filtered and concentrated under reduced pressure yields a crude residue. Flash chromatography with hexane: ethyl acetate (4:1) gives the title compound (10.4 g, 62 % yield) 1NMR(CDCl3):δ7.59 (d, J=8.5 Hz,1H),δ7.33 (t, J=8,1H),δ 7.20(m,3H),δ6.94(d, J=8.5 Hz,2H),δ5.12(s,2H),δ3.68(s,3H),δ3.58 (s,2H)

EXAMPLE 72

[4-(2-Pyridin-3-yl-benzyloxy)-phenyl]-acetic acid methyl ester



[0245] (4-(2-Bromo-benzyloxy)-phenyl)-acetic acid methyl ester (0.62g, 2mmol), 3-pyridyl-benzeneboronic acid (0.540g, 2 mmol), potassium phosphate(1.28 g, 6.03 mmol) and (1-1-Bis-(diphenylphosphinferrocene)dichloropalladium (II) (0.0816g,0.1 mmol) are dissolved in ethylene glycol diethyl ether (6.4 mL) and heated at 70° C overnight. The reaction is directly placed on a flash column and is eluted with hexane: ethyl acetate (2:1) to give the title compound (0.049 g, 7.3% yield). 1 H (400 MHz) (CDCl3) :δ8.67 (b,1H),δ8.50 (b,1H),δ7.75(d, J=6 Hz.1H),δ7.63(b,1H),δ7.46(m,2H),δ6.34(m,2H),δ7.15 (d, J=7.9 Hz,2H),δ6.81(d, J=9.9 Hz,2H),δ4.89 (s,2H),δ3.68 (s,3H)

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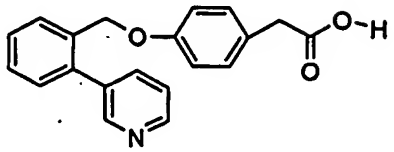
EXAMPLE 73

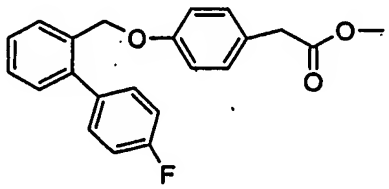
[4-(2-Pyridin-3-yl-benzyloxy)-phenyl]-acetic acid



[0246] (4-(2-Bromo-benzyloxy)-phenyl)-acetic acid methyl ester (0.049 g, 0.15 mmol) is dissolved in THF (2mL), Lithium hydroxide (0.011 g, 0.460mmol) dissolved in water (2mL) is added and the reaction is heated at 70° C for four hours. The reaction is acidified with 1 N HCl and extracted with ethyl acetate. The organic layers are combined and are washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration gives the title compound. mass spectrum (m/e) 320.1 (M+1).

EXAMPLE 74

(4-(4'-Fluoro-biphenyl-2-ylmethoxy)-phenyl)-acetic acid methyl ester



[0247] (4-(2-Bromo-benzyloxy)-phenyl)-acetic acid methyl ester (0.624 g, 2 mmol) ,4-Fluorobenzene boronic acid (0.616g, 4.4 mmol), potassium phosphate (1.28g, 6.03 mmol), 1,1 Bis-(diphenylphosphinferrocene)dichloropalladium (II) (0.0.816g, 0.1 mmol) is suspended in ethylene glycol diethyl ether (96.4 mL) and heated at 70° C for 16 hours. The reaction is partitioned between saturated sodium bicarbonate solution and

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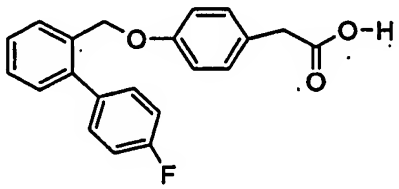
ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives a crude solid. The solid is columned on silica gel using hexane: ethyl acetate (95:5) and gradually increasing the polarity with hexane:ethyl acetate (80:20) : (1 H NMR,400 MHz, CDCl3) : δ7.61 (m,1H),δ7.42-7.31(m,5H), δ7.17 (d,J=12.8 Hz,2H), δ7.08 (t, J=10.3 Hz,2H), δ6.83(d, J=10.3 Hz, 2H), δ4.88 (s,2H) ,δ3.69 (s,3H), δ3.56 9s,2H)

EXAMPLE 75

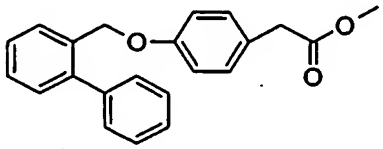
(4-(4'-Fluoro-biphenyl-2-ylmethoxy)-phenyl)-acetic acid



[0248] (4-(4'-Fluoro-biphenyl-2-ylmethoxy)-phenyl)-acetic acid methyl ester (0.340g, 1.01 mmol) is dissolved in THF (5 mL), and Lithium hydroxide (0.073g, 3.03 mmol) dissolved in water (1 mL), is added and stirred for several hours. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layers are washed with brine and dried over sodium sulfate. The solvent is filtered and concentrated under reduced pressure to give the title compound. mass spectrum (m/e) : 335.3 (M-1)

EXAMPLE 76

(4-(Biphenyl-2-ylmethoxy)-phenyl-acetic acid methyl ester



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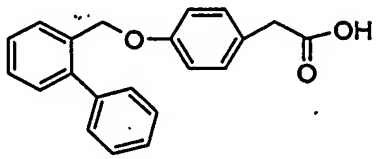
[0249] (4-(2-Bromo-benzyloxy)-phenyl)-acetic acid methyl ester (1.24 g, 4mmol) and benzene boronic acid (1.46 g, 12 mmol) and (1-1 Bis-(diphenylphosphine ferrocene)dichloropalladium (II) (0.163 g,0.2 mmol), and potassium phosphate (2.56 g,12.1 mmol) are suspended in ethylene glycol diethyl ether (12.8 m L) and heated at 70° C for 16 hours. The reaction is partitioned between ethyl acetate and water and purified by flash chromatography using hexane : ethyl acetate (95:5) as eluent, and increasing the polarity gradually to hexane: ethyl acetate (8:2) gives the title compound (1.0 g,75 %) 1H (400 MHz, CDCl3) :δ 7.62 (b,1H), δ7.34-7.42 (m,7 H),δ7.25 (J=10 Hz, t),δ7.16 (d, J=10.2 Hz,2H),δδ6.83 (d, J=11.2 Hz,2H),4.93 (s,2H),δ3.68 (s,3 H),δ3.56 (s,2 H)

EXAMPLE 77

(4-(Biphenyl-2-ylmethoxy)-phenyl-acetic acid



[0250] (4-(Biphenyl-2-ylmethoxy)-phenyl-acetic acid methyl ester (1.00 g, 3.00 mmol) is dissolved in THF (20mL) and lithium hydroxide (0.215 g, 9.00 mmol) dissolved in water (10 mL) is added and heated at 65° C for 4 hours. The reaction is allowed to stir an additional 16 hours at room temperature and is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and is dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives the title compound. mass spectrum : (m/e) 317.0 (M-1)

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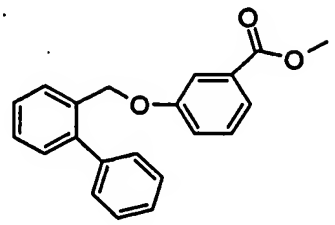
EXAMPLE 78

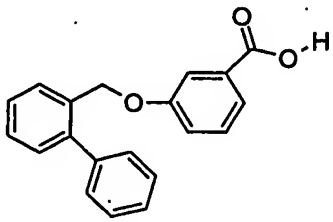
3-(Biphenyl-2-ylmethoxy)-benzoic acid methyl ester



[0251] Biphenyl-2-yl-methanol (0.616 g, 3.24 mmol), (0.492 g, 3.24 mmol (4-Hydroxy-phenyl)-acetic acid (0.492 g, 3.24 mmol) and triphenylphosphine (1.70 g, 6.48 mmol) are dissolved in THF (8m L). To this is added DEAD (1.12 g, 6.48 mmol) dissolved in THF (2 mL) dropwise and the reaction is stirred for 16 hours. The reaction is quenched with the addition of 1 N HCl and is extracted with ethyl acetate. The reaction is washed with brine and is dried over sodium sulfate. The organic layer is filtered and concentrated under reduced vacuum to give a crude residue. The crude residue is purified with flash chromatography with hexane : ethyl acetate (90:10) and increasing the polarity with hexane: ethyl acetate (85:15) gives the title compound. (1H NMR, CDCl3) : δ 7.65(b,2H), δ7.57 (b,1H), δ7.45- δ7.30 (m, (H), δ7.08 (b, 1H)) , δ5.01 (s,2H), δ3.91 (s, 3H)

EXAMPLE 79

3-(Biphenyl-2ylmethoxy)-benzoic acid



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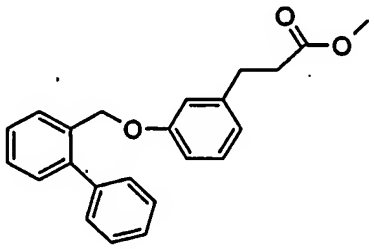
[0252] 3-(Biphenyl-2-ylmethoxy)-benzoic acid methyl ester (0.372g, 1.17 mmol) is dissolved in THF(10mL) and is heated at 50° C for 3 hours. The reaction is acidified with 1N HCl and is extracted with ethyl acetate. The reaction is washed with brine and is dried over sodium sulfate. The organic layer is filtered and concentrated under reduced pressure to give an oil. The oil is triturated with hexane : ether to give the title compound. mass spectrum : (m/e) 303.1 (M-1)

EXAMPLE 80

3-(3-(Biphenyl-2-ylmethoxy)-phenyl)-propionic acid methyl ester



[0253] Biphenyl-2-yl-methanol (0.616 g, 3.24 mmol), 3-(3-Hydroxy-phenyl)-propionic acid methyl ester (90.58 g,3.24 mmol) , triphenylphosphine (1.70g, 6.48 mmol) and DEAD(1.72g,6.48 mmol) are dissolved in THF (8 mL) and are stirred for 16 hours. The reaction is acidified with the addition of 1 N HCl and is extracted with ethyl acetate and washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure yields a crude oil. The oil is purified by flash chromatography with hexane:ethyl acetate (9 :1) to give the title compound (0.350 g, 31 %) : (1H 400 MHz, CDCl3) : δ7.62 (b,1H), δ7.43- δ7.32 (m,9 H), δ7.15 9t, J=7.2 Hz,1 H), δ6.76(d, J=4.7 Hz,1 H),δ6.71 (d,7.12 Hz,1H),δ 4.93 (s,2 H), δ3.65 (s,3H), δ2.88 (t,J=9.6 Hz, 2H), δ2.58 (t, J=9.6 Hz,2H)

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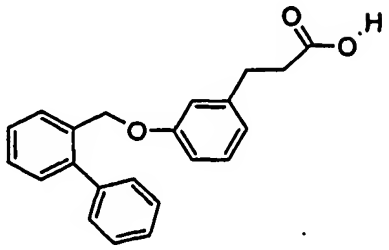
EXAMPLE 81

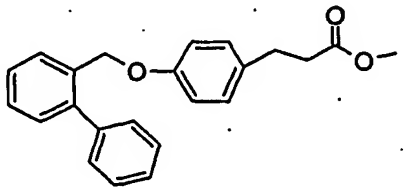
3-(3-(Biphenyl-2ylmethoxy)-phenyl)-propionic acid



[0254] 3-(3-(Biphenyl-2-ylmethoxy)-phenyl)-propionic acid methyl ester (0.350 g, 1.01 mmol) is dissolved in THF (10 mL), and lithium hydroxide (0.080 g, 3.33 mmol) dissolved in water (1 mL) is added and the reaction is heated at 55° C overnight. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate and concentrated under reduced pressure to give an oil. The oil was triturated with hexane : ether to give the title compound (0.209 g, 59 % yield). mass spectrum : 303.1 (M-1)

EXAMPLE 82

3-(4-(Biphenyl-2ylmethoxy)-phenyl)-propionic acid methyl ester



[0255] Biphenyl-2-yl-methanol (0.359 g, 1.89 mmol), 3-(4-Hydroxy-phenyl)-propionic acid methyl ester (0.340 g,1.89 mmol), triphenylphosphine (0.991 g, 3.78 mmol) and DEAD (0.647 g, 3.78 mmol) is dissolved in THF (6.8 mL) and stirred for 16 hours. The reaction is quenched with 1 N HCl and is extracted with ethyl acetate. The

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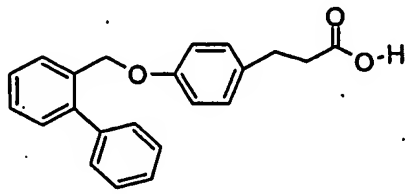
organic layer is washed with brine and dried over sodium sulfate and concentrated under reduced pressure gives an oil. The oil is purified by flash chromatography with hexane : ethyl acetate (9:1) and increasing the polarity with hexane : ethyl acetate (85:15) gives the title compound (0.108 g, 17 % yield). (1H ,CDCl3,400 MHz) δ7.62 (b,1H),δ 7.41-7.31(m,8H),δ7.06 (d, J=8.7 Hz,8 H),δ7.06 (d,J=8.7 Hz,2H),δ6.78(d,J=8.7 ,2H),δ4.91(s,2H),δ3.65(s,3H),δ2.87 (t ,J=7.5 Hz),2H),δ2.58 (t,J=7.5 Hz,2H)

EXAMPLE 83

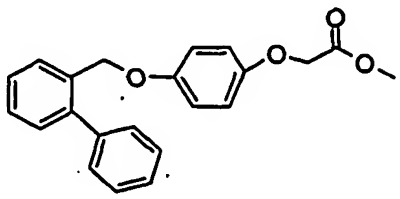
3-(4-(Biphenyl-2-ylmethoxy)-phenyl)-propionic acid



[0256] 3-(4-Hydroxy-phenyl)-propionic acid methyl ester (0.108g, 0.312 mmol) is dissolved in THF (3 mL) and lithium hydroxide (0.025 g, 1.03 mmol) in THF (2 mL) is added and heated at reflux for 1 hour. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate, filtration and concentration gives the title compound. mass spectrum (m/e) : 331.1 (M+1)

EXAMPLE 84

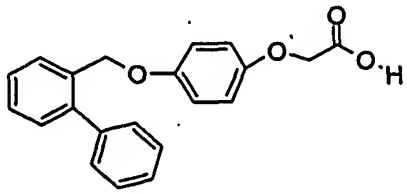
(4-(Biphenyl-2-ylmethoxy)-phenoxy-acetic acid methyl ester



[0257] Biphenyl-2-yl-methanol (0.359g, 1.89 mmol), (4-Hydroxy-phenoxy)-acetic acid methyl ester (0.344 g, 1.89 mmol), triphenylphosphine (0.991 g, 3.77 mmol) and DEAD (0.647g, 3.78 mmol) are dissolved in THF (6.8 mL) and stirred for 16 hours. The reaction is acidified with 1 N HCl and extracted with ethyl acetate and washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration gives an oil. The oil is purified by flash chromatography using hexane: ethyl acetate (9:1) to give the title compound (0.069g, 10 % yield). (1 H NMR, 400 MHz, CDCl3) :δ 7.60 (b,1H); δ7.42-7.32 (m,8H),δ6.80 (b,4H)δ.4.89 (s,2H),δ4.57 (s,2H),δ3.79 (3H,s)

EXAMPLE 85

(4-(Biphenyl-2-ylmethoxy)-phenoxy)-acetic acid

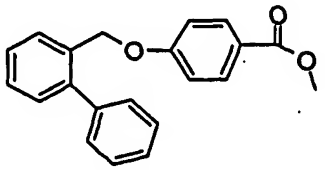


[0258] (4-(Biphenyl-2-ylmethoxy)-phenoxy-acetic acid methyl ester (0.066g, 0.197 mmol) is dissolved in 3 ml of THF, and Lithium hydroxide (0.016g, 0.651 mmol) dissolved in water (1mL) is added and the reaction and heated at 55° C for 6 hours. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate and is washed with

brine. The organic layer is dried over sodium sulfate and filtered, followed by concentration under reduced pressure to yield the title compound (0.056 g, 85%): mass spectrum : (m/e): 333.2 (M-1)

EXAMPLE 86

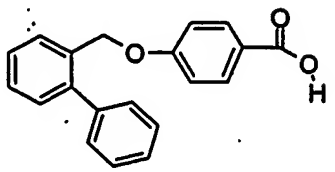
4-(Biphenyl-2-ylmethoxy)-benzoic acid methyl ester



[0259] Biphenyl-2-yl-methanol (0.254g, 1.34 mmol), 4-Hydroxy-benzoic acid methyl ester (0.203 g, 1.34 mmol) and triphenylphosphine (0.703 g, 2.68mmol) are dissolved in THF (3.3 mL) and is cooled in an ice bath and DEAD (0.467 g, 2.68 mmol) is added and the reaction is stirred for 16 hours. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and is dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives a crude oil. The oil is chromatographed using hexane : ethyl acetate (9:1) and increasing the polarity to hexane : ethyl acetate (85:15) to give the title compound (0.297 g,70 %) : (1 H NMR ,400 MHz,CDCl3) : 7.94 (d,J=9 Hz,2H),7.51 (b,1H), 7.43-7.33 (m,8 H),6.86(d, J=9 Hz,2 H),5.00 (s,2H),3.83 (s,3H)

EXAMPLE 87

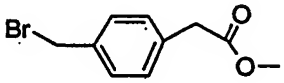
4-(Biphenyl-2-ylmethoxy)-benzoic acid



[0260] 4-(Biphenyl-2-ylmethoxy)-benzoic acid methyl ester (0.294 g, 0.923 mmol) is dissolved in THF (6mL) and lithium hydroxide (0.073 g, 3.05 mmol) is dissolved in water (2 mL) and is heated at 55° C for 16 hours. Lithium hydroxide (0.070 g, 2.92 mmol) is added and the reaction is heated an additional 3 hours. The reaction is partitioned between ethyl acetate and water. The aqueous layer is acidified with 1 N HCl and extracted with ethyl acetate and washed with brine. The organic layer is dried over sodium sulfate then filtered and concentration under reduced pressure yields the title compound. mass spectrum (m/e) :303.1 (M-1)

EXAMPLE 88

(4-Bromomethyl-phenyl)-acetic acid methyl ester

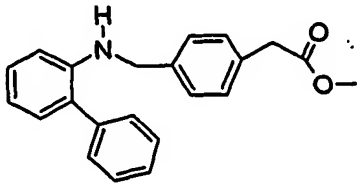


[0261] (4-bromomethyl-phenyl)-acetic acid (0.229 g, 1 mmol) and DMF (2 mL) was suspended in dichloromethane (6 mL) and cooled in an ice water bath. Oxalyl chloride (0.127 g, 1 mmol) was added dropwise. Methanol (6 mL) is added and the ice bath was then removed. The reaction is judged to be complete by TLC. The reaction is partitioned between dichloromethane and water. The organic layer is washed with saturated sodium bicarbonate and by brine. The organic layer is dried over sodium

sulfate and filtered. Concentration under reduced pressure gives the title compound (0.200 g, 83 %) . (1 NMR, 400 MHz,CDCl3) : 7.25 (d, J=7.5 Hz,2H),7.29 (m,2 H),4.58 (s,1H),4.48 (s,1 H),3.69 (s,3H),3.52 (m,2H)

EXAMPLE 89

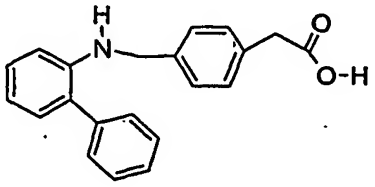
(4-(Biphenyl-2-ylaminomethyl)-phenyl-acetic acid methyl ester



[0262] Biphenyl-2-ylamine (0.150 g, 0.886 mmol), potassium carbonate (0.122g,0.884 mmol) and (4-Bromomethyl-phenyl)-acetic acid methyl ester (0.196 g,0.806 mmol) and is heated at 50° C. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate. The organic layer is filtered and concentrated under reduced pressure to give an oil. The oil is chromatographed using hexane : ethyl acetate (95:5) to yield the title compound (0.053 g, 18 %) mass spectrum : (m/e) 331.9 (M-1)

EXAMPLE 90

(4-(Biphenyl-2ylaminomethyl)-phenyl)-acetic acid methyl ester

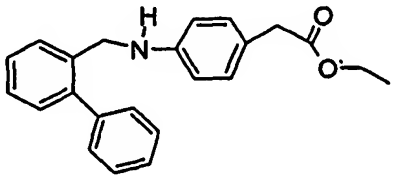


[0263] (4-(Biphenyl-2-ylaminomethyl)-phenyl-acetic acid methyl ester (0.053 g, 0.159 mmol) is dissolved in THF (3 mL) and lithium hydroxide (0.0115 g, 0.479 mmol)

dissolved in 1 water (1mL) is added and the reaction is heated at 55° C 16 hours. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate and the organic layer is washed with brine and dried over sodium sulfate. The reaction is filtered and concentrated under reduced pressure to give an oil. The oil is triturated with ether, ethyl acetate and hexane to give a solid which after filtration and drying gives the title compound. mass spectrum (m/e) : 317.9 (M+1)

EXAMPLE 91

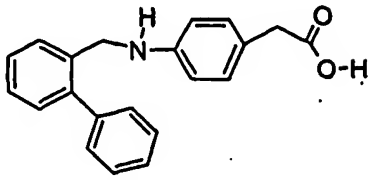
(4-((Biphenyl-2-ylmethyl)-amino)-phenyl)-acetic acid ethyl ester



[0264] 2-Bromomethyl-biphenyl (0.247 g,1mmol), potassium carbonate (0.152 g,1.1 mmol) and (4-Amino-phenyl)-acetic acid ethyl ester (0.197 g,1.1 mmol) is dissolved in DMF (3 mL) and heated at 50° C for 16 hours. The reaction is partitioned between ethyl acetate and water and washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives an oil. The oil is chromatographed on hexane : ethyl acetate (95:5 hexane :ethyl acetate) and gradually increasing the polarity with hexane ; ethyl acetate (9:1) to give the title compound (0.166g, 48 % yield). mass spectrum (m/e) 346.0 (M+1)

EXAMPLE 92

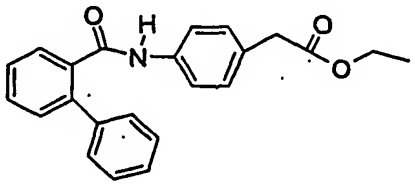
((4-((Biphenyl-2-ylmethyl)-amino)-phenyl)-acetic acid



[0265] (4-((Biphenyl-2-ylmethyl)-amino)-phenyl)-acetic acid ethyl ester 90.16g, 0.481 mmol) is dissolved in ethanol (3ml) and 1 N Sodium hydroxide solution is added and the reaction is heated at 50° C for 1 ½ hours. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives the title compound. mass spectrum : (m/e) 317. (M+1)

EXAMPLE 93

(4-((Biphenyl-2-carbonyl)-amino)-phenyl)-acetic acid ethyl ester

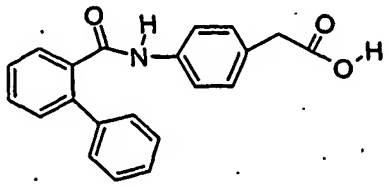


[0266] Biphenyl-2-carboxylic acid (0.991 g, 5mmol) ,(0.985g, 5.5 mmol) and catalytic DMF is added together and cooled in an ice bath. Oxalyl chloride (0.698g, 6.98 mmol) is added dropwise. The ice bath is removed and warm water bath is placed underneath. The reaction is judged to be complete by TLC after twenty minutes. (4-Amino-phenyl)-acetic acid ethyl ester (0.985g, 5.5 mmol) dissolved in dichloromethane (10 mL) is added. Triethylamine (1.52 g, 15.0 mmol) is added and the reaction is allowed

to stir for 16 hours. The reaction is partitioned between dichloromethane and water. The organic layer is washed with brine and dried over sodium sulfate .The organic layer is filtered and concentration under reduced pressure yields a beige solid. The solid is stirred with diethyl ether and the solid is filtered off to give the title compound. (1.17 g, 65 % yield) mass spectrum (m/e) 360.0(M+1).

EXAMPLE 94

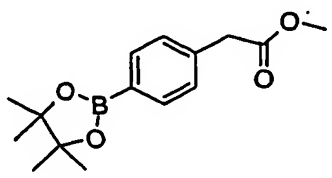
(4-((Biphenyl-2-carbonyl)-amino)-phenyl)-acetic acid



[0267] (4-((Biphenyl-2-carbonyl)-amino)-phenyl)-acetic acid ethyl ester (1.07g, 2.97 mmol) is dissolved in ethanol (15 mL). 1 N NaOH (8.9 mL) is added and the reaction is heated at 90° C for 4 hours. The reaction is acidified with 1 N HCl and the resulting precipitate is filtered off and dried to give the title compound. mass spectrum (m/e) 332.0 (M+1)

EXAMPLE 95

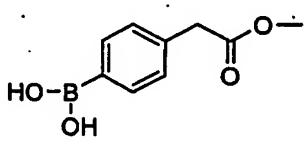
(4-(4,4,5,5-Tetramethyl-(1,3,2)dioxaborolan-2-yl)-phenyl-acetic acid methyl ester



[0268] Bis pinacol-diboron (2.53 g, 9.96 mmol), 4-Bromo-phenyl)-acetic acid methyl ester (1.52 g, 6.64 mmol) (1-1 Bis-(diphenylphosphine ferrocene)dichloropalladium (II) (0.271g, 0.332mmol), diphenylphosphine ferrocene (0.135 g) and potassium acetate (2.04 g,20.78 mmol) are suspended in dioxane (18 mL). The reaction is heated at 80° C for 16 hours. The reaction is partitioned between ethyl acetate and water. The reaction is washed with brine and dried over sodium sulfate. The reaction is filtered and the organics are removed under reduced pressure to obtain an oil. The oil is flash columned using hexane : ethyl acetate (95:5) and gradually increasing the polarity with hexane : ethyl acetate (90 :10) to give the title compound (1.78 g, 94 % yield). (1 H NMR,400 MHz, CDCl3): δ7.77 (d, J=7.6 Hz,2 H),δ7.29 (d, J=7.6 Hz,2 H),δ3.68 (s,3H).δ3.64 (s, 2H),δ1.33 (s,6H), δ1.25 (s,6H)

EXAMPLE 96

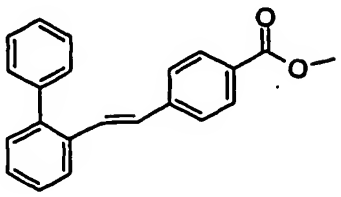
(4-Phenylboronic acid)-acetic acid-methyl ester



[0269] (4-(4,4,5,5-Tetramethyl-(1,3,2)dioxaborolan-2-yl)-phenyl-acetic acid methyl ester is dissolved in acetone (180 mL) and 0.1 N ammonium acetate solution (124 mL) and sodium periodate (3.99g,18.7 mmol) are added and the reaction is stirred overnight. The reaction is acidified with 1 N HCl and partitioned between ethyl acetate and water. The reaction is washed with brine and dried over sodium sulfate. The organic layer was filtered and the solvent was concentrated under reduced pressure to give the title compound (0.680g.57 %). mass spectrum : (m/e) :190.9 (M-1)

EXAMPLE 97

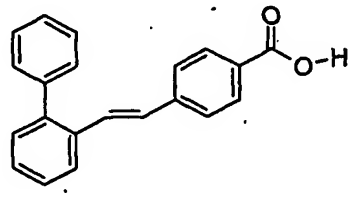
E-4-(2-biphenyl-2-yl-vinyl)-benzoic acid methyl ester



[0270] 4-Vinyl-benzoic acid methyl ester (0.324g,2 mmol), Biphenyl-2-bromide (0.324g,2.04 mmol), tri –o-tolyltriphosphine (0.061 g,0.2 mmol), Tris(dibenzylidene acetone) dipalladium (0) (0.054g,0.06mmol) and triethylamine (0.212g,2.10 mmol) is suspended in DMF (6mL) and heated at 100° C for 36 hours. The reaction is columned on silica gel using hexane : ethyl acetate (95:5) and increasing the polarity with hexane: ethyl acetate (9:1) to give the title compound (E isomer) (0.340g, 52% yield). (1 H NMR –CDCl3): 7.96 (d,J=10.4 Hz,2 H),7.77 (d,J=6.9 Hz,1H),7.47 –7.36 (m,10H) , 7.23 (d,J= 17.3 Hz,1H),7.06 (d,J=17.3 Hz,1H), 3.91(s,3H)

EXAMPLE 98

4-(2-Biphenyl-2yl-vinyl)-benzoic acid

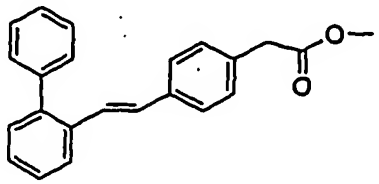


[0271] E-4-(2-Biphenyl-2-yl-vinyl)-benzoic acid methyl ester (0.160g, 0.509 mmol) is dissolved in THF(2 mL) and lithium hydroxide (0.036 g,1.52 mmol dissolved in water (1 mL) is added and the reaction is heated at 55° C. The reaction is acidified with 1 N HCl and is extracted with ethyl acetate. The organic layers are washed with

brine and dried over sodium sulfate. The organic layer is filtered and concentration under reduced pressure gives the title compound . mass spectrum : (m/e) 299.2 (M-1)

EXAMPLE 99

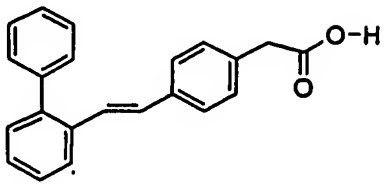
(4-(2-Biphenyl-2-yl-vinyl)-phenyl)-acetic acid methyl ester



[0272] (4-Vinyl-phenyl)-acetic acid methyl ester (0.186 g, 1.15 mmol),Biphenyl-2-bromide (0.273g,1.17 mmol), o-tolyl-triphenylphosphine (0.35,0.12 mmol), Tris(dibenzylidene acetone) palladium (0) (0.321g, 0.351 mmol) and triethylamine (0.122g, 1.20mmol) are suspended in DMF(3 mL) and heated at 100° C for 2 hours. The reaction is partitioned between ethyl acetate and 1 N HCl and the organic layers are combined and washed with brine and dried over sodium sulfate. The reaction is filtered and the reaction is concentrated under reduced pressure to give an oil. The oil is columned using hexane: ethyl acetate (95:5) and increasing the polarity with hexane :ethyl acetate (90:10) to give the title compound (0.160g, 42 % yield) (1 H NMR, 400 MHZ, CDCl3) : δ7.75 (q,J=8.1 Hz,),δ7.64 (m,1H), δ7.46-7.32 (m,10H),δ7.20 (d,J=8 HZ,1H),δ7.05 (d,J=16.1 Hz),δ7.01 (d,J=16.1 Hz,1H),δ3.63 (s,3H),δ3.61(s,2H)

EXAMPLE 100

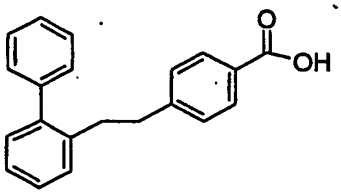
(4-(2-Biphenyl-2-yl-vinyl)-phenyl)-acetic acid



[0273] (4-(2-Biphenyl-2-yl-vinyl)-phenyl)-acetic acid methyl ester (0.16 g, 0.48 mmol) is dissolved in THF (3 mL) and lithium hydroxide (0.035 g, 1.44 mmol) dissolved in water (1 mL) is added and the reaction is heated at 55° C for 16 hours. The reaction is acidified and is extracted with ethyl acetate. The organic layer is washed with brine and dried over sodium sulfate and filtered and concentration under reduced pressure to give title compound. mass spectrum: (m/e) 314.0 (M-1)

EXAMPLE 101

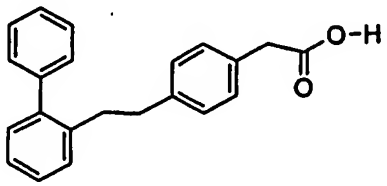
4-(2-Biphenyl-2-yl-ethyl)-benzoic acid



[0274] 4-(2-Biphenyl-2yl-vinyl)-benzoic acid (0.083g, 0.28 mmol) is dissolved in ethanol (5 mL) and the reaction is hydrogenated in a Paar® Bottle under 30 psi for 4 hours. The reaction is filtered through Celite ® and the ethanol is removed under reduced pressure to give the title compound. mass spectrum (m/e) 301.2 (M-1)

EXAMPLE 102

(4-(2-Biphenyl-2-yl-ethyl)-phenyl)-acetic acid



[0275] 4-(2-Biphenyl-2-yl-vinyl)-phenyl)-acetic acid (0.025 g,0.08 mmol) is dissolved in ethanol (5mL) and is hydrogenated in a Paar® Bottle under 30 PSI for 4hours. The reaction is filtered through Celite ® and removal of the ethanol under reduced pressure gives the title compound. mass spectrum : (m/e) 315.2 (M-1)

EXAMPLE 103

Co-transfection assay

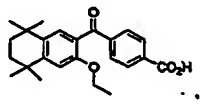
[0276] CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum (CH-FBS) then transferred to 96-well microtiter plates one day prior to transfection.

[0277] To determine HNF-4α receptor agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by FuGENE 6 transfection reagent in 175 cm2 flask with the following plasmids: pCMX-HNF-4αDF (3ug/flask), apoA1-LUC reporter (1ug/flask), and filler DNA (pcDNA; 3ug/flask). The receptor plasmid, pCMX-HNF-4αDF, contains the rat HNF-4α1 under constitutive control of the CMV promoter, as more fully described in J.D. Fraser *et al.*,

"DNA binding and transcription activation specificity of hepatocyte nuclear factor 4" *NAR*, 26: 2702-2707 (1998).

[0278] The reporter plasmid, apoA1-LUC, contains the cDNA for firefly luciferase (LUC) under control of a multimerized HNF-4α response element (the A site from the apo A1 promoter) linked to the TK minimal promoter. See *e.g.*, Fraser *et al.* supra. Twenty four after transfection the cells are harvested and plated in 96 well plates at 10,000 cells/well. Media containing one of the modulator compounds of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

[0279] Samples containing 4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoic acid (LG0100695), which had previously been found to have agonist activity on HNF-4α, were included as a reference agonist. LG0100695 has the following structure:



[0280] After 24 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC activity using a NORTHSTAR HTS workstation.

[0281] The mean and standard error of the mean (SEM) of the luciferase response were calculated. Data were plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist LG0100695. Antagonist

activity was determined by testing the amount of LUC expression in the presence of no exogenous compound (just the endogenous ligand) as HNF-4α receptor agonist. The concentration of a test compound that inhibited 50% of LUC expression was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

Table 1: Agonist, partial agonist, antagonist activity of HNF-4α receptor modulator compounds of present invention. Efficacy (%) for HNF-4α agonist was determined by comparing activity (*e.g.*, luciferase production) of putative agonist to that LG0100695. Efficacy (%) for HNF-4α antagonist was determined by the percentage amount by which the luciferase production is reduced (maximum concentration of antagonist) from the luciferase production without compound.

Cmpd	K_i	HNF-4α Agonist CV-1 Cells		HNF-4α Antagonist CV-1 Cells	
No.		Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)
1	500	126	1820		
15	1150	43	2422		
33	360	100	1496		
37	391	59	2644		
40	426	58	1549		
45	281	81	2118		
49	936			57	59
52	428	27	1525		
53	1658	46	3002		
68	120	35	1552		

[1] K_i and potency given in nM

[0282] The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0283] While in accordance with the patent statutes, description of the various embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

[0284] Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented merely to illustrate certain embodiments of the present invention.